Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research

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Contents

INTRODUCTION

In March 1994, the National Institutes of Health (NIH) published its **NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research** in the *Federal Register*. These guidelines (Appendix A of this document), which address issues concerning the recruitment of women and minorities and their subpopulations in clinical research and especially clinical trials, were developed in response to requirements stated in Subtitle B of Part I of the NIH Revitalization Act of 1993 (Public Law 103-43). As part of these requirements, NIH must engage in efforts to recruit women and minorities into these studies. Section 131 of the Act states that:

> *The Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in projects of clinical research.*

The goal of this legislation is to increase the opportunities for obtaining critically important information with which to enhance health and treat disease among all Americans—and to detect and account for significant differences between genders or racial and ethnic groups where they exist.

In order to accomplish this task, investigators and their staffs must appropriately recruit and retain participants of both genders as well as diverse racial and ethnic groups in studies. The process of inviting individuals to participate and remain in a study requires a broad knowledge base encompassing behavior theory (Rimer et al. 1993, Green et al. 1980, von Winterfeldt and Edwards 1986). Investigators will therefore need to draw upon different theories, depending upon the nature of the research, the characteristics of the population of interest, and the settings in which they are encountered.

As part of its campaign to integrate these new guidelines into the biomedical and behavioral research infrastructure, the NIH has developed this notebook, a primer, outlining key issues in the recruitment and retention of individuals into studies. ***The suggestions presented in this notebook are not requirements that must be incorporated into research applications/proposals.*** They are presented to provide guidance to investigators and their research teams as they consider the scientific question(s), study design, and methods to facilitate appropriate enrollment of study participants.

How to Use This Notebook

The NIH recognizes that these guidelines will take some time to be understood and assimilated into the research community. This notebook is one step in that process and serves as a complement to the **NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research**.

Because participants are necessary for many different types of studies, outreach efforts necessarily span the entire clinical research spectrum, from the smallest observational studies and Phase I-II clinical trials, recruiting five or 10 participants, to the largest Phase III clinical trials enrolling thousands. Primary prevention studies involving apparently disease-free individuals, as well as secondary and tertiary intervention involving individuals with diagnosed disease are included, as are studies in which the unit of observation is the entire community.

The notebook does not tell investigators whether they need to enroll participants from various populations, nor is it a step-by-step guide through recruitment and retention. Rather, it furnishes advice on inclusion criteria in the form of a decision tree, provides an overview of key elements in the outreach process, and suggests a number of practical applications, including ethical considerations. Attention to these factors in the design of a research project will assist in the appropriate inclusion of women and minorities into studies. ***The presentation of information and the suggestions included in the notebook are not requirements for grant or contract applications.***

For more information on outreach, readers should consult the Reference section at the end of this notebook. Because some important and relevant documents may have been missed, readers are urged to conduct their own search of the literature, and seek out other resources for guidance and expertise relevant to their particular study questions.

This primer is an evolving document that will be reviewed and revised in the future. Therefore, NIH staff welcome your comments for future editions of this notebook, particularly case studies that describe successful and effective strategies.

Factors to Consider in Determining Inclusion of Women and Minorities and their Subpopulations in Clinical Research

In deciding to what extent women and minorities should be included in a study and what outreach efforts are necessary to achieve appropriate participation, it is essential that the investigator carefully review the scientific question(s) or hypotheses. The need for incorporation of women and minority subpopulations will derive from the scientific question(s). As such, the investigator should consider the following questions.

- Is the scientific question or hypothesis applicable equally to both genders and to all minority groups and their subpopulations?

- Is the condition under study more prevalent or severe in one particular group?

- Have sufficient studies already been performed in one or more groups, leaving gaps that can be filled by focusing the research on certain population groups?

Having considered these questions, the investigator may next turn attention to the following questions.

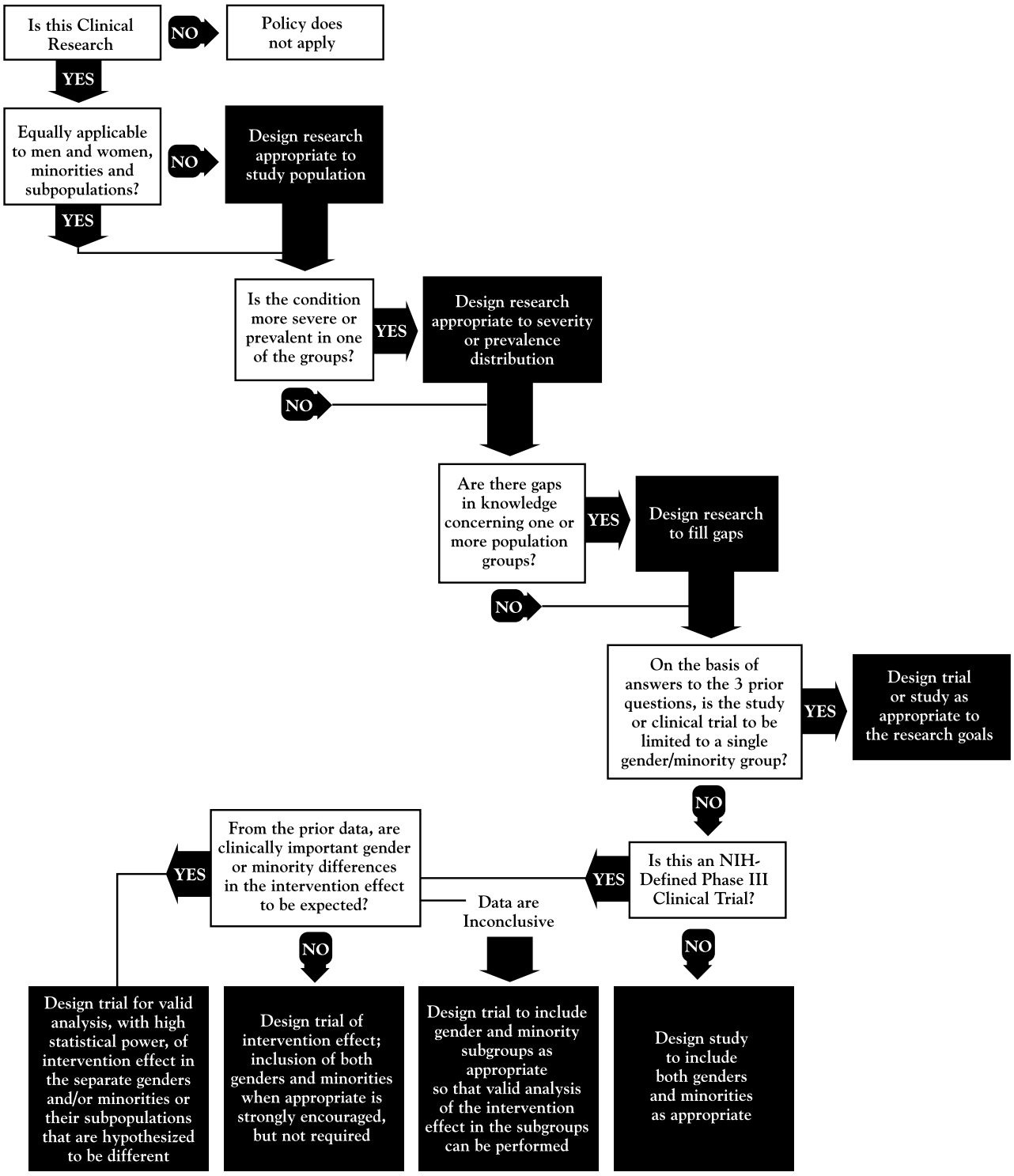
- Can the need for appropriate diversity be met by obtaining access to participants from a single clinic or facility? Will oversampling of certain groups be possible?

- If a single clinic or facility is not adequate, can the needed participants be enrolled by going to hospitals or other clinical facilities in the nearby geographic region?

- If demographic limitations preclude answering scientific questions locally in the appropriate gender and minority groups, is it feasible or necessary to expand the geographic area, or to establish satellite centers?

A "decision tree" follows which may provide further guidance in determining inclusion for clinical research as well as Phase III clinical trials. To obtain a graphic interpretation of the decision tree, please address your requests to the senior extramural staff member of a particular NIH institute or center listed on page 14513 of the *Federal Register* (March 28, 1994), or to the Office of Research on Women's Health, or the Office of Research on Minority Health (page 14508 of the *Federal Register*). A copy of the *Federal Register* notice is reprinted in Appendix A of this notebook.

Decision Tree for Inclusion of Women and Minorities in Clinical Research*



*Clinical Research is defined as all research involving human subjects. See policy for more detailed definition.

A Decision Tree for the Inclusion of Women and Minorities in Clinical Research[1]

1. **Is this Clinical Research?** (Clinical Research is defined as all research involving human subjects. See policy for detailed definition.)

   - If YES, proceed to the next question.

   - If NO, the policy does not apply.

2. **Is the scientific question or hypothesis equally applicable to both men and women, and to minorities and their subpopulations?**

   - If NO, design the research appropriate to the study population.
   Proceed to the next question.

   - If YES, proceed to next question.

3. **Is the condition more severe or prevalent in one of the groups?**

   - If YES, design the research appropriate to the severity or prevalence distribution.
   Proceed to the next question.

   - If NO, proceed to next question.

4. **Are there gaps in knowledge concerning one or more population groups?**

   - If YES, design the research to fill the gaps. Proceed to the next question.

   - If NO, proceed to next question.

[1] *NOTE: The text contained here is also available in a graphic decision tree. If the graphic is not included in this version of the notebook (e.g. obtained from the NIH Guide), you may obtain the graphic version of the decision tree by addressing your request to the senior extramural staff from one of the NIH Institutes or Centers listed at the end of the NIH Guidelines on page 14513 of the* Federal Register *(March 28, 1994), to the Office of Research on Women's Health, or to the Office of Research on Minority Health (page 14508 of the* Federal Register*); the* Federal Register *reprint is contained in Appendix A of this notebook.*

5. **On the basis of answers to questions 2,3, and 4, is the study or clinical trial to be limited to a single gender/minority group?**

- If YES, design the trial or study as appropriate to the research goals.

- If NO, proceed to next question.

6. **Is this an NIH-Defined Phase III Clinical Trial?**

- If NO, design study to include both genders and minorities as appropriate.

- If YES, proceed to next question.

7. **From the prior data, are clinically important gender or minority differences in the intervention effect to be expected?**

- If YES, design trial for valid analysis, with high statistical power, of intervention effect in the separate genders and/or minorities or their subpopulations that are hypothesized to be different.

- If NO, design trial of intervention effect; inclusion of both genders and/or minorities when appropriate is strongly encouraged, but not required.

- If data are INCONCLUSIVE, design trial to include gender and minority subgroups as appropriate so that valid analysis of the intervention effect in the subgroups can be performed.

Elements of Outreach

The five elements of outreach described below are based on reviews of the literature, ongoing NIH-sponsored studies, recent workshops, and numerous group discussions. These elements should be considered in the recruitment and retention of women and racial or ethnic groups into clinical studies across the entire spectrum of biomedical and behavioral research. The operational details may differ when individuals are recruited in hospitals, clinics, or other health care centers, rather than from the general community (work sites, schools, places of worship), but the underlying elements of understanding, communication, and evaluation are common to all successful outreach efforts.

1. **Understand the Study Population.** Identify the potential research participants, the medical settings in which they are found, and/or the community in which they reside. This may require an assessment of racial/ethnic characteristics, socioeconomic status, age, gender, family configuration, language, education/literacy levels, community structure, cultural norms, migration patterns, points of access (sites of intervention), and needs and values of the potential research participants, including reasons for seeking health care.

2. **Establish Explicit Goals.** Having determined the scientific question(s) for investigation and the study design, establish specific goals for recruiting and retaining study participants. Where possible, involve formal and informal decision makers, organizations, and institutions, as well as the main communication channels in each medical setting or community. Establish lines of communication and cooperation to promote continuing awareness of and trust in the project.

3. **Achieve Agreement on Research Plans.** Confirm that the investigators, medical and health care staff, and community all agree to the design, methodologies, implementation, and completion of the study.

4. **Design and Conduct Evaluations.** Design and implement an evaluation plan to assess the efficacy of recruitment and retention strategies. In cooperation with health care staff or community leaders and potential participants, pretest and periodically retest the recruitment and retention strategies—including resources, incentives, and problem-solving mechanisms—to ensure that they conform with the needs and values of the research participants and their communities. Monitor subject accrual on a frequent and regular basis and compare results with established goals.

5. **Establish and Maintain Communication.** Establish mechanisms for keeping all those involved in the study (research staff, health care providers, participants and their families and communities) apprised of progress and study findings. This will not only increase understanding and awareness of the project, but will also acknowledge the fact that the participants and their health care setting or community are valuable partners in the scientific process.

Element 1
Understand the Study Population

Identify the potential research participants, the medical settings in which they are found, and/or the community in which they reside. This may require an assessment of racial/ethnic characteristics, socioeconomic status, age, gender, language, education/literacy levels, community structure, cultural norms, migration patterns, points of access (sites of intervention), and needs and values of the potential research participants, including reasons for seeking health care.

WHY IS THIS IMPORTANT?

Working in culturally diverse settings can be challenging for even the most experienced clinical investigator. One key to success is to learn as much as possible about the groups of interest. Gathering background information about the potential study populations and their communities is an essential first step, to be followed by periodic updates of this information (NHLBI, 1993a; Chen, 1993).

Hospitals and clinics represent a special type of community and should be approached as one would any community. There may be important differences, however. For example, research-based alcoholism after-care programs may have to compete with established service programs for the same population of patients—and their personal or insurance payments.

Background information on the potential study populations and their surroundings is important. ***Investigators should note, however, that while suggestions are provided in a wide range of subpopulations, that the NIH Guidelines do not require that every study include each racial and ethnic group. The scientific question must determine the inclusion criteria.***

Considerable heterogeneity often exists within health care settings and communities. Socioeconomic, cultural, and linguistic characteristics can vary widely, along with major differences in health beliefs and practices. Recruitment and retention strategies must therefore be based on the background information about the particular groups of interest. For example, the label "Southeast Asian" does not take into consideration the major differences among Filipino, Hmong, Laotian, Vietnamese, and Cambodian peoples. The term "Native Americans" is used to describe more than 500 federally recognized tribes. Similarly, "Hispanic/Latino" populations have different ethnic origins and racial characteristics and should not necessarily be considered as constituting a single subpopulation.

Country of origin, immigration status, language, and acculturation add to the wide diversity within racial and ethnic populations, and support the need to conduct a careful assessment of the population of interest (Johnson et al., 1992). Furthermore, in communities where individuals may be wary of free communication, such as those with illegal immigrants or where illegal activities are in evidence, investigators will need special skills to evaluate the population.

The successful recruitment and retention of women in studies requires consideration of several important factors. Women of childbearing potential must understand the requirements of the study and decide whether it is appropriate for them to participate (e.g., do the benefits outweigh the risks). Even with institutional review board approval, the research team must make special efforts to ensure that women who are considering participation fully understand the demands of the study and what they will be asked to do. Informed consent is essential. Indeed, issues of autonomy are paramount in the decision to participate. In some instances, women may wish to share their decision to participate in a study with family members or others in the community.

Other factors affect the ability of women of different ages and family statuses to participate and should be weighed when designing recruitment and retention strategies. Child care, location of the research site and ease of access and transportation, and time off work are only a few of these considerations.

If the research study requires the inclusion of individuals in a particular geographical region, investigators must know the infrastructure and the characteristics of the health care setting, the different communities within the region, and a perspective on the region itself. Is it a rural or an urban community? What are the various cultural groups living there? In which cities or neighborhoods does each ethnic or cultural group live? What are the structure and characteristics of local health care systems and settings?

Investigators also need to gain insights about how community residents, or hospital and clinic staff, perceive the research team and its home institution. Such information is crucial in identifying potential problems and finding ways to avoid or work through them early in the outreach efforts.

HOW DO I APPROACH IT?

Depending on the study questions and research setting, the assessment process requires data. A number of those components are presented here. Several sources describe orderly assessment procedures for learning about the individuals, health care settings, and communities of interest (NCI, 1992; NHLBI, 1993b; Braithwaite et al., 1989; Randall-David, 1989).

- Identify characteristics of the potential participants and setting(s).

  – *Individual characteristics:* age, gender, cultural norms, education, literacy, language, health awareness, reasons for seeking medical care, knowledge of available health care services, ideas and attitudes about disease, health beliefs and practices, beliefs in effectiveness of interventions, beliefs in susceptibility of disease, access to health care, sensitivity of health care providers, religious beliefs, sexual preferences, and acculturation patterns.

  – *Family characteristics:* family structure, number and age of children and other family members, number of parents and head of household, socioeconomic level, beliefs and practices, cultural norms, education, literacy, language, health awareness, and access to health care.

  – *Employment characteristics:* work patterns (daytime versus night-shift work), part- versus full-time employment, willingness of employers to grant leave time for participation, and willingness of employees to take leave time for participation.

  – *Community characteristics:* socioeconomic level, urban or rural background, migration patterns, racial and ethnic minority groups residing in the community, health care delivery systems, and business and community structure.

- Identify contacts and points of access that potential participants might utilize.

  – *Health care decision makers:* physicians (especially referring physicians), nurses, department chairs, hospital administrators, research committees, and institutional review boards (IRBs).

  – *Community leaders:* not only political figures and government officials but also clergy, tribal leaders, teachers and principals, leaders of business and community groups, media personalities, sports figures, and youth leaders.

– *Community businesses and organizations:* schools, day-care centers, places of worship, colleges and universities (including fraternities and sororities), hospitals, clinics, nursing homes, women's and men's clubs, senior and community centers, and private organizations (e.g., American Heart Association, American Cancer Society), alumni associations, recreational facilities (e.g., gyms, local recreational centers) and work sites (including grocery and clothing stores, beauty parlors and barber shops, laundromats, restaurants, taverns, pharmacies, and fire and police stations).

– *Social service agencies:* public welfare, Women, Infants, and Children (WIC), tribal councils, community action agencies, public housing, community health clinics, mental health clinics, and drug treatment centers.

- Identify communication channels.

  – *Formal interpersonal relationships:* health care providers, religious leaders, community leaders, and school teachers.

  – *Informal interpersonal relationships:* family, friends, and those who are related by language or common origins, other researchers in the hospital or clinic, former students, and other contacts.

  – *Mass media:* newspapers, magazines, films, radio, and television.

Language is a vital part of communication, and investigators from outside a particular community may not be familiar with the meaning of expressions common within a community or with the nuances of colloquial expressions. Another integral part of this process is a clear understanding of the literacy levels of participants. This literacy level must be ascertained for the individual in her or his first language and in English. As such, special efforts may be needed to develop and translate informational materials and other instruments so that they are sensitive to the linguistic and cultural differences among genders and subpopulations (e.g., Hispanic/Latino subpopulations and Asian subpopulations [Chen et al., 1992a,b]).

In general, the research staff and institution must be aware of their abilities and limitations working with the diversity of participants identified for the study (e.g., gays and lesbians, drug users and abusers, AIDS patients, older individuals, minorities [Giachello et al., 1992]).

Element 2
Establish Explicit Goals

Having determined the scientific question(s) for investigation and the study design, establish specific goals for recruiting and retaining study participants. Where possible, involve decision makers, organizations, and institutions, as well as the main communication channels in each medical setting or community. Establish lines of communication and cooperation to promote continuing awareness of and trust in the project.

WHY IS THIS IMPORTANT?

The development and implementation of effective recruitment and retention strategies is a multidimensional and evolving process. Outreach strategies that are productive in one population or setting may be counterproductive in another. Consequently, it is essential to involve the health care setting and/or community early in the design of outreach strategies. Hospital and/or clinic staff and community leaders and organizations are important sources of perspective on potential participants. They can provide insights into problems in study design that would otherwise become barriers to the successful accrual of the participants. Forging linkages with these individuals and organizations will strengthen lines of communication, establish trust, and promote awareness (Mellins et al., 1992).

- Many people of color are skeptical about participating in clinical studies. Abuses of the past are well known and have been cited by individuals as reasons for refusing to take part in a clinical study. The Tuskeegee Syphilis Study, for example, was a tragic deception well remembered even today. Opinion leaders can become the primary link to these groups and individuals, providing reassurance, and building trust.

- Leaders can inform investigators about the social and economic needs of the population. For example, the provision of basic social services has been shown to be an effective mechanism for overcoming barriers to the recruitment and retention of women and underserved populations in AIDS clinical trials in the inner cities. When payments or other incentives are offered, however, they should not be of such a magnitude as to be coercive. The level at which this occurs varies with the characteristics of the population.

- Consultation with hospital or clinic staff and formal and informal community leaders may allow investigators to "fine-tune" their recruitment and retention strategies to reflect differences among individuals and groups of interest. For example, Mexicans, Puerto Ricans, Cubans, and Central or South Americans may share a common language, but may differ in culture and values (Shumaker et al., 1992).

HOW DO I APPROACH IT?

Many mechanisms exist to establish explicit goals for appropriate recruitment and retention; several suggestions are presented here.

- Identify recruitment and retention goals as specifically and explicitly as possible, with the collaboration of hospital or clinic staff and community leaders.

- Involve hospital/clinic staff and/or community leaders and local organizations early in the process. For example, present the study plans to physicians and others in the health care settings. Consider creating an advisory board comprised of study staff, health care providers (where warranted), and participants and community members as soon as the study begins.

- Include one or more representative(s) from the hospital or clinic staff as members of the research team to serve as liaisons between the researchers, the staff, and the participants.

- Offer hospital or clinic staff and/or community organizations opportunities to participate at different levels of involvement, from establishing and taking part in focus groups, to providing sponsorship for the study, to assisting in recruiting, to contributing to the writing or reviewing of proposals.

- Recruit women and minority investigators and health care staff for the project. Consider subcontracting specific components of the research activities to hospital or clinic staff and/or community organizations.

- Ask advisory boards to review the research plans to ensure that incentives are appropriate for the individuals, that no undue coercion is used, and that materials are appropriate in terms of language and literacy levels.

Element 3
Achieve Agreement on Research Plans

Confirm that the investigators, medical and health care staff, and/or community all agree to the design, methodologies, implementation, and completion of the study.

WHY IS THIS IMPORTANT?

Women and minorities must be included in clinical research if scientists are to make valid inferences about health and disease in these groups. It is essential that investigators strive to build the level of understanding and trust that will lead to a productive partnership and successful conduct of the research project.

HOW DO I APPROACH IT?

Many mechanisms exist to achieve agreement; several are presented here.

- Consult the hospital or clinic staff and/or the community at every stage of the study. It is much easier to achieve agreement on issues if all parties have been involved from the earliest stages. Mutually beneficial collaboration can be achieved, and maintained for many years, if the hospital's, clinic's, and community's needs, concerns, and recommendations are taken into account. Involve the hospital or clinic staff and/or community in the planning, as well as the conduct of the research. Understanding and responding to individual and group concerns can lead to more appropriate and useful results.

- Present the proposed study, complete with rationale and plans for implementing it, to those who are expected to recruit subjects or answer public questions. This can be accomplished through announcements in public forums in the hospital, clinic, or community, and through announcements in hospital and community newsletters and in special mailings. Do not use jargon in describing the proposed research.

- Create an advisory board that includes key members of hospital or clinic staff and community organizations. This can be a very effective mechanism for establishing and maintaining a functional study. Not only can an advisory board guide sensitive and sensible recruitment, it can also assist in understanding and reenlisting those who drop out of the study.

- Find ways of including and rewarding hospital or clinic staff so that they find the research to be a satisfying and interesting activity, rather than an additional burden.

Element 4
Design and Conduct Evaluations

Design and implement an evaluation plan to assess how well the recruitment and retention strategies are working. In cooperation with community leaders, health care staff, and potential participants, pretest and periodically retest the recruitment and retention strategies—including resources, incentives, and problem-solving mechanisms—to ensure that they conform with the needs and values of the research participants and their communities. Monitor subject accrual on a frequent and regular basis and compare results with established goals.

Study design should include a process for systematically documenting the extent to which recruitment and retention objectives were accomplished during a defined period of time for a defined population. Such an evaluation will help investigators to (1) determine which strategies work well; (2) certify the degree of progress that has occurred; and (3) identify elements that are not working. Windsor et al. (1984) have identified several relevant forms of evaluation, including formative, process, short- and long-term outcome, and impact evaluation (see Glossary).

WHY IS THIS IMPORTANT?

Evaluation is an integral part of developing and planning the recruitment and retention strategies (NCI, 1992). As such, evaluation provides investigators with tools for the following tasks:

- Addressing the issues of feasibility: Can the goals be accomplished with the existing staff and resources within the time frame specified?

- Addressing the issues of accountability to the research institutions, research participants and their families, and the community.

- Providing information to encourage the acceptance and response of the community and research participants involved.

- Providing a feedback mechanism to guide changes in current strategies to avoid or counter participant drop out.

HOW DO I APPROACH IT?

Depending upon the type of evaluation being conducted, important elements form the basis for evaluation. Investigators wishing to learn more about any of the different types of evaluation are urged to consult the many texts prepared on the subject or to seek guidance from an expert. Because this can be a complex process, only the most general elements are presented here.

- Establish evaluation measures.

  – *Study staff:* time-line schedules, work performed, and response to participants over time.

  – *Media outreach:* publicity, promotion, type and extent of media coverage, estimated audience size and demographics, and materials planned and distributed.

  – *Population response:* volume of inquiries, screening participation rates, and interviewees' perceptions of screening and proposed study and staff.

  – *Enrollment rates:* proportion of eligible subjects who agree to participate.

  – *Continuing functions and response:* number of phone calls or meetings with community-based organizations, advisory boards, focus groups, and other patient or participant groups.

  – *Compliance:* participants' continuing responses to study protocols and demands.

  – *Feedback:* consultation with and responses from research participants, community leaders, and hospital or clinic staff.

- Make use of the evaluation data to refine the recruitment and retention strategies.

  – Are there objectives that are not being met? Why?

  – Are there strategies or activities that are not succeeding? Why?

  – Are more resources required, or can resources be used more efficiently?

  – What are the strengths and weaknesses of the strategies or mechanisms for retaining study participants?

- Establish an ongoing, problem-solving mechanism. This should include not only regularly scheduled meetings with participant focus groups and hospital or clinic staff involved in the study, but also adequate mechanisms for tracking patients and investigating each patient withdrawal to determine if some aspect of the retention strategy is at fault. Investigators may also need to provide counseling to address the social needs that can impede the participation of women and members of minority groups in a clinicial study (e.g., child care, transportation costs, study site location, availability of parking). Above all, investigators must remain flexible within the constraints of the study goals and objectives.

Before initiating the full-scale project, investigators typically find it useful to conduct a pilot test of the proposed recruitment/retention strategies. This will allow the opportunity to test the feasibility of the planned approach and amend it according to feedback from the study population. Potential participants can contribute valuable information on the needs, cultures, and values of the population of interest and the community in which they reside. It is during this preliminary test period that the investigator can best determine the most cost-effective distribution of resources, including materials, equipment, personnel, and time. Based on this information, fiscal and budgetary planning can be finalized and problem-solving mechanisms can be put in place (Rand et al., 1992).

Pilot testing strategies can also provide feedback on proposed strategies and incentives, such as educational materials, hiring staff from the proposed study population, establishing a project office in the community, providing transportation, and other compensations (e.g., meals, food coupons, child care, or cash). Problem-solving mechanisms instituted following the pilot study can include regularly scheduled reviews to identify barriers that are interfering with compliance or continued participation.

Periodic retesting and refining of recruitment and retention strategies can also be important, for the following reasons.

- Resources can vary during the course of the study, so it may be prudent to identify alternative mechanisms in advance. Should problems arise, local agencies or organizations may serve as backups. By the same token, members of the research team may need to take over some of the recruitment functions if they prove too time-consuming for hospital or clinic staff.

- Community leaders and hospital or clinic staff can assist in determining the most appropriate distribution of resources—for example, instances where volunteers may be used in lieu of paid staff and the availability of bilingual and sign interpreters.

Element 5
Establish and Maintain Communication

Establish mechanisms for keeping all those involved in the study (research staff, health care providers, participants and their families and communities) apprised of progress and, ultimately, study findings. This will not only increase understanding and awareness of the project, but will recognize the participants and their health care setting or community as valuable partners in the scientific process.

WHY IS THIS IMPORTANT?

Effective communication of study results is another important element in building trust in the community. Researchers must remember, however, that their professional priorities may conflict with the priorities of study participants. Specifically, publication of research results in scientific journals has little value to participants and could be perceived as exploitive unless the same results are also conveyed to the participants, and their communities, in a sensitive manner (Shumaker et al., 1992). Providing the community and the hospital or clinic staff with a detailed report on the progress of research is often the first step in developing a long-term relationship of trust and cooperation. Future relationships with these populations could depend on whether they perceive their role as that of partners in the research or merely "guinea pigs."

Communication of study results should therefore be among the ethical considerations of any research project (see below). Dissemination of research findings can also promote awareness of social, medical, and educational resources that have been made available a result of the project.

HOW DO I APPROACH IT?

The following avenues of communication can be used not only for announcing the study and recruiting participants, but also for disseminating study results (Rand et al., 1992). The important point is that participants, their health care providers, and their communities understand the outcome of the study and that their inestimable contribution is noted and appreciated.

- Formal methods of communication can be used through the media, including radio (e.g., talk shows, ethnic language stations, and public service announcements), print (e.g., flyers, posters, hospital newsletters, and newspaper articles in language appropriate to the proposed study group), and television (e.g., talk shows, news shows, cable access channels, and ethnic language stations).

- Informal methods of communication can be utilized by including personal contact (e.g., telephone, door-to-door, neighborhood events, schools, staff meetings) and multiple sites of intervention (e.g., health clinics, social service agencies, hospitals and clinics, places of worship, union halls, senior citizen centers, shelters, grocery stores, beauty shops, and day care centers).

- At the conclusion of the study, the research team may wish to host a special presentation for participants, hospital or clinic staff, and community groups to discuss the outcome of the study and its subsequent application to health.

- Feedback mechanisms can and should be utilized in the participants' language to ensure ongoing success and retention of participants and that follow-up questionnaires reach participants. Study results should also be provided at the completion of the study, along with the appreciation of the principal investigator and staff.

- Consider employing an outreach educator, whose responsibilities might include:

  – setting up monthly meetings with health care or community-based organizations and developing linkages to enhance research participation and to "trouble-shoot" problems;

  – developing and preparing health care or community-oriented educational materials;

  – attending health care or participant meetings, community health fairs or block parties to periodically disseminate study information;

  – providing requested information about the research study to individuals and health care and/or community groups through educational presentations and workshops;

  – providing in-service training and guidance to all investigative staff, to ensure that they are sensitive to the needs, attitudes, and concerns of study participants;

  – providing education and training to health care and/or community leaders to ensure that they understand the benefits and demands of research and the role participants and their health care setting and/or communities play in such collaboration; and

  – convening periodic meetings of scientific staff and health care and/or community leaders (or advisory board) to assess retention and to devise strategies for countering drop out and bolstering retention and protocol adherence.

Ethical Issues

Any research involving human subjects raises ethical issues that demand consideration and resolution. The requirement to include women and minorities may increase the difficulties presented by these issues, but this does not contravene the responsibility of investigators to anticipate and deal with ethical concerns. When studies are conducted in communities, community leaders, both formal and informal, should be consulted regarding the proposed study and its intended and unintended consequences. The procedures for seeking approval from the Institutional Review Board must be followed.

In interpreting the mandate for outreach in the recruitment and retention of women and racial and/or ethnic groups into clinical studies, investigators and their staff members must respect the three basic ethical principles established by the Belmont Report (National Commission, 1978):

1. **Respect for persons.** This principle incorporates two ethical convictions: first, individuals should be treated as autonomous agents; and second, persons with diminished autonomy are entitled to protection. When investigators conduct research involving human beings, respect for the rights of the individual requires that the participant enter into the research voluntarily and with adequate information.

2. **Beneficence.** This principle stipulates that persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Two complementary expressions of beneficent actions have been formulated: (1) do no harm; and (2) maximize possible benefits while minimizing possible harm.

3. **Justice**. This principle stipulates that injustice occurs when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly. When investigators recruit subjects for research, they should not systematically include some individuals or groups because of their easy availability, their compromised position, or their malleability. Rather, subjects should be recruited based on their relation to the problem being studied.

In short, while investigators should recruit participants who will provide the most useful, valid, and widely generalizable knowledge about the problem being studied, they should not recruit participants only because they are available, malleable, or in a compromised position. By the same token, however, participants should not be denied access for reasons unrelated to their health status or the purposes of the study.

It should also be assumed that all of the regulations of the NIH Office of Protection from Research Risks (OPRR) concerning ethical considerations in clinical and community trials apply to *all* individuals (human subjects) regardless of their gender, race, or ethnicity. However, successful implementation of these regulations depends on the ability of the research team to understand implications of conducting research in particular populations, settings, and trials.

Potential participants in clinical and community trials differ in ways that can affect their comprehension of the purpose, benefits, and risks of the study, as well as their capacity to adhere to the study protocol. Research has shown that a participant's understanding of design elements, such as randomization and placebo group, may be affected by race and educational level; other barriers to full participation (e.g., transportation costs, inflexible work schedules, availability of child care, literacy, and competency in English) may also present barriers to participation and require consideration. Issues of autonomy are paramount in the decision to participate. As such, allowing time for potential participants to become fully informed about what their participation entails is essential. Translators may be required, and potential participants may need several sessions to ask questions and understand procedures. In some instances, women may wish to share their decision to participate in a study with family members or others in the community.

Similarly, "coercion" requires interpretation in terms of a particular target population. Some participants may need reimbursement for costs incurred in the course of their participation, but the prospect of reimbursement should not become such an inducement that the potential participant feels compelled to participate for economic reasons.

Seven Points of Consideration for Institutional Review Boards

To assist in consideration of ethical issues by Institutional Review Boards (IRBs), the Office of Protection from Research Risks recently released a document which listed seven key points (OPRR REPORTS, 1994).

Institutions and IRBs have the following responsibilities:

1. To help ensure that investigators understand the importance of inclusion of both genders and minorities in research and clearly delineate the expectations for the design and conduct of such research. They should assist in providing investigators with written guidance and educational opportunities for clarification.

2. To specify that, when scientifically appropriate, investigators cite evidence or lack of evidence if a health situation or intervention in the proposed research may affect one gender or minority group differently and describe how the proposed research addresses that evidence. Investigators should be prepared to describe the extent to which both genders and persons of various ethnic and racial backgrounds are or have been involved in similar research.

3. To help create guidelines for investigators to facilitate recruitment and retention of participants to ensure representation and sufficient involvement of targeted populations. The extent to which investigators are collaborating with researchers at other institutions that can involve increased numbers of men or women or populations from different minority groups must be part of the information the IRB reviews, particularly with regard to Phase III clinical trials.

4. To ensure that any special vulnerabilities of participants (e.g., educational level, socioeconomic status) are accounted for and handled appropriately. The IRB should carefully consider if reimbursements (cash and material provisions) are appropriate to the context of the proposed research, with particular attention to ensure that these reimbursements do not promote coercion or undue influence to participate or remain in the study.

5. To safeguard the consent process and to promote open and free communication between the researcher and the participants. Investigators and IRBs must seek to understand cultural nuances and types of foreign languages inherent in the populations to be enrolled. The possibility of illiteracy among potential research participants must also be considered and assurances given that adequate provision has been made for the appropriate translations of the consent documents or the availability of translators.

6. To arrange for inclusion of women and members of minority groups on the IRB, especially if the nature and volume of the research to be conducted at the institution routinely includes these populations. IRBs should also consider consulting ad hoc advisors who could help with understanding the perspectives of various groups. Also, institutions and IRBs can encourage investigators to seek out such perspectives during the planning of research protocols.

7. To specify that NIH-supported investigators provide details of the proposed involvement of humans in the research, including the characteristics of the subject population, anticipated numbers, age ranges, and health statuses. The proposed research should specify the gender and racial and/or ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation. If ethnic, racial, and gender estimates and continuing review numbers are not included in the background data for a protocol, the investigators must provide a clear rationale for exclusion of this information.

Where Do I Go for Help?

- **Start With a Literature Search.**

  – Census data and other government reports and statistics can be helpful in identifying potential research participants, as well as the specific problems and needs potential participants may have in comparison with the general population. For example, the National Health Interview Survey (NHIS) and the National Health and Nutrition Examination Survey (NHANES), as well as several other national and periodic surveys, provide important and timely data on individuals and groups.

  – Medical and public health references, especially epidemiology and health intervention articles, address issues of recruitment and retention for the specific group of interest in the research study. A sampling of such articles is included in the Reference section at the end of this notebook.

  – Behavioral and social science literature focuses on intercultural and ethnic studies, including psychosocial, sociocultural, and anthropological references specific to various racial, ethnic, and cultural groups. Such information can be useful in providing a general understanding of various cultures' values, beliefs and practices, and historical experiences in the United States.

  – Local newspapers are a good source of information about a community. The local news and editorial sections of newspapers can provide very specific information about a community (i.e., the issues community members consider most pressing, their concerns, and problems). These sources also provide listings of current and upcoming community events.

- **Consult With Experts.**

  – Other researchers who have investigated the same areas of scientific interest or who have personal experience with a specific ethnic and/or racial group or with women as study participants are invaluable sources of information and guidance.

  – Health professionals or other persons working in similar communities or with similar problems can provide useful perspectives. Often such experts are available through local, regional, or national health-related and community organizations that have relevant experience with various groups.

  – Individuals and groups from the place or community of interest can play crucial roles in helping to design, promote, and maintain interest in the research study.

- **Consider Other Methods for Understanding the Community.**

  – *Researcher observation*. The researcher can participate as an observer in a variety of community activities, such as organization meetings, community social gatherings, cultural ceremonies, and/or special celebrations.

  – *Informal conversation*. This method allows the scientific team the opportunity to gather information in a less formal manner. Such encounters require thoughtful and careful listening to capture accurate information (history, anecdotes, perspectives) about the people and the community.

  – *Case study or in-depth interview*. This method allows for more detailed information about a person's life, family, neighborhood, and community history and perspective.

  – *Focus group and surveys*. While these two inquiries are quite different in the information produced, they are useful in developing culturally relevant strategies. Such inquiries can reveal the range of community attitudes and beliefs about a problem, people's perceived needs and priorities, and their preferences for strategies and formats.

- **Federal Resources.**

  – Senior NIH extramural staff who can provide information about the relevant policies and programs in their respective institutes and centers are listed at the end of the *Federal Register* notice in Appendix A.

In addition, the Federal government has a number of agencies that maintain information and data bases: the Centers for Disease Control and Prevention, especially the National Center for Health Statistics, the Health Services and Resource Administration, the Agency for Health Care Policy and Research, the Health Care Financing Administration. These and other government resources can be accessed by calling a central information number or by writing to each agency.

NIH Review Criteria for the Inclusion of Women and Minorities Into Clinical Research

In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections and review committees), technical evaluation groups, and intramural review panels will be instructed to consider the following elements in the recruitment and retention of women and minorities in clinical research.

- Evaluate the proposed plan for the inclusion of women and minorities and their subpopulations for appropriate representation or evaluate the proposed justification when representation is limited or absent.

- Evaluate the proposed exclusion of women and minorities and their subpopulations on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects.

- Evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research.

- Determine whether the design of a clinical trial is adequate to measure potential differences.

- Evaluate the plans for recruitment, retention, and outreach for study participants.

These criteria, which apply to the full range of NIH-supported clinical research, are a part of the scientific assessment and will contribute to the assigned priority score.

The plans for recruitment and retention for study participants should be clearly presented in terms of the methods and mechanisms for outreach. Peer Review Group members will look for evidence that the investigator has addressed the inclusion of women and minorities and their subpopulations in a satisfactory manner.

Such evidence might include, for example, information on the population characteristics of the disease or condition under study; national and local demographics of the population; knowledge and understanding of the racial, ethnic, and cultural characteristics of the population and relevant scientific literature; prior experience, success, and collaborations in recruitment and retention of

the populations and subpopulations to be studied; and the plans, arrangements, and letters of commitment from relevant community groups and organizations for the planned study. Plans should also consider appropriate staffing needs for recruitment, retention, and outreach plans.

The composition of any study group should be based on science, and not on the convenience of the investigator. It is not necessarily expected that every study will include representation from all racial or ethnic groups. For single hospital, clinic and university studies, it is important to distinguish between data on the characteristics of the population served by the site compared with the broader community or regional population. To avoid selection bias, planned enrollment should be viewed in terms of the demographics of the disease or condition in the broader community or regional or national population, rather than local demographics or referral patterns. For multicenter trials, the combined enrollment from all recruitment sites may achieve the appropriate gender and racial and/or ethnic composition for the study. Study designs involving oversampling to achieve the needed balance of groups may be appropriate in some circumstances.

Applicants must provide information using the summary table below for planned enrollment of women and minorities, and awardees will report annually on the planned enrollment for the approved project and the actual enrollment after receipt of the award and the start of the project.

TABLE 1: GENDER AND MINORITY INCLUSION (398/2590)

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female							
Male							
Unknown							
Total							

Note: (1) For planned studies, indicate the expected study composition using the categories noted in the table. If there is more than one study, provide a separate table for each study. In addition, report on the subpopulations which are included in the study. (2) For ongoing studies, provide the number of subjects enrolled in the study to date (cumulatively since the study began) according to the same categories and table format.

Glossary

Acculturation: Degree to which people from a particular cultural or ethnic group display behavior that reflects the influence of pervasive, mainstream norms of behavior.

Assimilation: Extent to which an individual enters a new culture and becomes a part of it. Includes both the motivation of the individual to enter the mainstream culture and the extent to which members of the mainstream culture welcome or discourage the entry and inclusion of that person in the mainstream culture.

Clinical Trial, Phase III: A broadly based prospective clinical investigation for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Community-based organizations: Organizations that have their origins or basis within the community and which utilize some aspect of the community's goals, mandate, or objectives as part of their efforts.

Communication channels: The means by which a message gets from a source to a receiver. Mass media channels are more effective in making people aware of a new idea; interpersonal channels are more effective in persuading people to adopt a new idea.

Cultural competence: A set of academic and interpersonal skills that allows individuals to increase their understanding and appreciation of cultural differences and similarities within, among, and between groups. This requires a willingness and ability to draw on community-based values, traditions, and customs and to work with persons who are knowledgeable about and from the community in developing focused interventions, communications, and other supports.

Cultural diversity: Differences in race, ethnicity, language, nationality, or religion among various groups within a community, organization, or nation. A city is said to be culturally diverse if its residents include members of different racial and/or ethnic groups.

Cultural sensitivity: Respect for ethnic individuals and for their culture; the recognition that such individuals have cultural health beliefs and practices; the integration of those beliefs and practices in the overall treatment plan for the patient; and the ability to act on behalf of the individual to assure quality health care.

Formative evaluation: Collects information about the components of the recruitment and retention aspects of the research project. Information from this type of evaluation can be used to test messages, select communications channels, and revise the communication process.

Impact evaluation*:* Focuses on the long-range results of the program and subsequent changes in health status. Impact evaluations are rarely possible because they are costly, involve extended commitment, and may depend upon other strategies in addition to the recruitment and retention component of the research project.

Mainstream: Used to describe the "general market," but usually refers to a broad population that, in the continental United States, is primarily white and middle class.

Multicultural: Designed for, or pertaining to, two or more distinctive cultures.

Outcome evaluation: Provides descriptive information on the project and can be used to document short-term results. Task-focused results describe the output of the activities (i.e., number of participants recruited as a result of a talk show in a local television station). Short-term results describe the immediate effects of the strategies on the target population (i.e., percentage of the target group that is participating in one of the research protocols).

Process evaluation: Documents the degree of implementation of the recruitment and retention activities. It describes how many items, of what materials, are provided to whom, by whom, and when and whether they responded. This type of evaluation may look at the origin of the research project, the methods used, the target population, program personnel/staff, and cost.

Race: A population of individuals who possess distinguishable physical characteristics that are genetically transmitted.

Site of intervention: A specific location used to establish contact with or gain access to subjects within the neighborhood or community in which they reside. Examples include schools, work sites, beauty shops, barber shops, ethnic grocery stores, small group meetings in people's homes, community clinics, hospitals, and day-care centers.

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Appendix A

NIH Guidelines

on the Inclusion of Women and Minorities as Subjects in Clinical Research

[*Federal Register,* Vol. 59 No. 59 (March 28, 1994), pp. 14508-14513]

National Institutes of Health

Monday
March 28, 1994

Part VIII

Department of Health and Human Services

National Institutes of Health

NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research; Notice

Department of Health and Human Services

National Institutes of Health

RIN 0905-ZA18

NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research

Editorial Note: This document was originally published at 59 FR 11146, March 9, 1994, and is being reprinted in its entirety because of typesetting errors.

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) is establishing guidelines on the inclusion of women and minorities and their subpopulations in research involving human subjects, including clinical trials, supported by the NIH, as required in the NIH Revitalization Act of 1993.

EFFECTIVE DATE: March 9, 1994.

ADDRESSES: Although these guidelines are effective on the date of publication, written comments can be sent to either the Office of Research on Women's Health, National Institutes of Health, Building 1, Room 203, Bethesda, MD 20892, or to the Office of Research on Minority Health, National Institutes of Health, Building 1, Room 225, Bethesda, MD 20892. During the first year of implementation, NIH will review the comments and experience with the guidelines in order to determine whether modifications to the guidelines are warranted.

FOR FURTHER INFORMATION CONTACT: Programmatic inquiries should be directed to senior extramural staff of the relevant NIH Institute or Center named at the end of this notice.

SUPPLEMENTARY INFORMATION: NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

I. Introduction

This document sets forth guidelines on the inclusion of women and members of minority groups and their subpopulations in clinical research, including clinical trials, supported by the National Institutes of Health (NIH). For the purposes of this document, clinical research is defined as NIH-supported biomedical and behavioral research involving human subjects. These guidelines, implemented in accordance with section 492B of the Public Health Service Act, added by the NIH Revitalization Act of 1993, Public Law. (Pub.L.) 103-43, supersede and strengthen the previous policies. NIH/ADAMHA Policy Concerning the Inclusion of Women in Study Populations, and ADAMHA/NIH Policy Concerning the Inclusion of Minorities in Study Populations, published in the NIH GUIDE FOR GRANTS AND CONTRACTS, 1990.

The 1993 guidelines continue the 1990 guidelines with three major additions. The new policy requires that, in addition to the continuing inclusion of women and members of minority groups in all NIH-supported biomedical and behavioral research involving human subjects, the NIH must:

- Ensure that women and members of minorities and their subpopulations are included in all human subject research;
- For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished;
- Not allow cost as an acceptable reason for excluding these groups; and,
- Initiate programs and support for outreach efforts to recruit these groups into clinical studies.

Since a primary aim of research is to provide scientific evidence leading to a change in health policy or a standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently. To this end, the guidelines published here are intended to ensure that all future NIH-supported biomedical and behavioral research involving human subjects will be carried out in a manner sufficient to elicit information about individuals of both genders and the diverse racial and ethnic groups and, in the case of clinical trials, to examine differential effects on such groups. Increased attention, therefore, must be given to gender, race, and ethnicity in earlier stages of research to allow for informed decisions at the Phase III clinical trial stage.

These guidelines reaffirm NIH's commitment to the fundamental principles of inclusion of women and racial and ethnic minority groups and their subpopulations in research. This policy should result in a variety of new research opportunities to address significant gaps in knowledge about health problems that affect women and racial/ethnic minorities and their subpopulations.

The NIH recognizes that issues will arise with the implementation of these guidelines and thus welcomes comments. During the first year of implementation, NIH will review the comments, and consider modifications, within the scope of the statute, to the guidelines.

II. Background

The NIH Revitalization Act of 1993, PL 103-43, signed by President Clinton on June 10, 1993, directs the NIH to establish guidelines for inclusion of women and minorities in clinical research. This guidance shall include guidelines regarding—

(A) the circumstances under which the inclusion of women and minorities as subjects in projects of clinical research is inappropriate * * *

(B) the manner in which clinical trials are required to be designed and carried out * * *; and

(C) the operation of outreach programs * * * 492B(d)(1)

The statute states that

In conducting or supporting clinical research for the purposes of this title, the Director of NIH shall * * * ensure that—

A. women are included as subjects in each project of such research; and

B. members of minority groups are included in such research. 492B(a)(1)

The statute further defines "clinical research" to include "clinical trials" and states that

In the case of any clinical trial in which women or members of minority groups will be included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial. 492B(C)

Specifically addressing the issue of minority groups, the statute states that

The term "minority group" includes sub-populations of minority groups. The Director of NIH shall, through the guidelines established * * * defines the terms "minority group" and "subpopulation" for the purposes of the preceding sentence. 492B(g)(2)

The statute speaks specifically to outreach and states that

The Director of NIH, in consultation with the Director of the Office of Research of Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in the projects of clinical research. 492B(a)(2)

The statute includes a specific provision pertaining to the cost of clinical research and, in particular clinical trials.

(A)(i) In the case of a clinical trial, the guidelines shall provide that the costs of such inclusion in the trial is (sic) not a permissible consideration in determining whether such inclusion is inappropriate. 492B(d)(2)

(ii) In the case of other projects of clinical research, the guidelines shall provide that the costs of such inclusion in the project is (sic) not a permissible consideration in determining whether such inclusion is inappropriate unless the data regarding women or members of minority groups, respectively, that would be obtained in such project (in the event that such inclusion were required) have been or are being obtained through other means that provide data of comparable quality. 492B(d)(2)

Exclusions to the requirement for inclusion of women and minorities are stated in the statute, as follows:

The requirements established regarding women and members of minority groups shall not apply to the project of clinical research if the inclusion, as subjects in the project, of women and members of minority groups, respectively—

(1) Is inappropriate with respect to the health of the subjects;

(2) Is inappropriate with respect to the purpose of the research; or

(3) Is inappropriate under such other circumstances as the Director of NIH may designate. 492B(b)

(B) In the case of a clinical trial, the guidelines may provide that such inclusion in the trial is not required if there is substantial scientific data demonstrating that there is no significant difference between—

(i) The effects that the variables to be studied in the trial have on women or members of minority groups, respectively; and

(ii) The effects that variables have on the individuals who would serve as subjects in the trial in the event that such inclusion were not required. 492B(d)(2)

III. Policy

A. Research Involving Human Subjects

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of a Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the composition of the proposed study population in terms of gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

B. Clinical Trials

Under the statute, when a Phase III clinical trial (see Definitions, Section V-A) is proposed, evidence must be reviewed to show whether or not clinically important gender or race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

As such, investigators must consider the following when planning a Phase III clinical trial for NIH support.

- If the data from prior studies strongly indicate the existence of significant differences of clinical or public health importance in intervention effect among subgroups (gender and/or racial/ethnic subgroups), the primary question(s) to be addressed by the

proposed Phase III trial and the design of that trial must specifically accommodate this. For example, if men and women are thought to respond differently to an intervention, then the Phase III trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

• If the data from prior studies strongly support no significant differences of clinical or public health importance in intervention effect between subgroups, then gender or race/ethnicity will not be required as subject selection criteria. However, the inclusion of gender or racial/ethnic subgroups is strongly encouraged.

• If the data from prior studies neither support strongly nor negate strongly the existence of significant differences of clinical or public health importance in intervention effect between subgroups, then the Phase III trial will be required to include sufficient and appropriate entry of gender and racial/ethnic subgroups, so that valid analysis of the intervention effect in subgroups can be performed. However, the trial will not be required to provide high statistical power for each subgroup.

Cost is not an acceptable reason for exclusion of women and minorities from clinical trials.

C. Funding

NIH funding components will not award any grant, cooperative agreement or contract or support any intramural project to be conducted or funded in Fiscal Year 1995 and thereafter which does not comply with this policy. For research awards that are covered by this policy, awardees will report annually on enrollment of women and men, and on the race and ethnicity of research participants.

IV. Implementation

A. Date of Implementation

This policy applies to all applications/proposals and intramural projects to be submitted on and after June 1, 1994 (the date of full implementation) seeking Fiscal Year 1995 support. Projects funded prior to June 10, 1993, must still comply with the 1990 policy and report annually on enrollment of subjects using gender and racial/ethnic categories as required in the Application for Continuation of a Public Health Service Grant (PHS Form 2590), in contracts and in intramural projects.

B. Transition Policy

NIH-supported biomedical and behavioral research projects involving human subjects, with the exception of Phase III clinical trial projects as discussed below, that are awarded between June 10, 1993, the date of enactment, and September 30, 1994, the end of Fiscal Year 1994, shall be subject to the requirements of the 1990 policy and the annual reporting requirements on enrollment using gender and racial/ethnic categories.

For all Phase III clinical trial projects proposed between June 10, 1993 and June 1, 1994, and those awarded between June 10, 1993 and September 30, 1994, Institute/Center staff will examine the applications/proposals, pending awards, awards and intramural projects to determine if the study was developed in a manner consistent with the new guidelines. If it is deemed inconsistent, NIH staff will contact investigators to discuss approaches to accommodate the new policy. Administrative actions may be needed to accommodate or revise the pending trials. Institutes/Centers may need to consider initiating a complementary activity to address any gender or minority representation concerns.

The NIH Director will determine whether the Phase III clinical trial being considered during this transition is in compliance with this policy, whether acceptable modifications have been made, or whether the Institute/Center will initiate a complementary activity that addresses the gender or minority representation concerns. Pending awards will not be funded without this determination.

Solicitations issued by the NIH planned for release after the date of publication of the guidelines in the Federal Register will include the new requirements.

C. Roles and Responsibilities

While this policy applies to all applicants for NIH-supported biomedical and behavioral research involving human subjects, certain individuals and groups have special roles and responsibilities with regard to the adoption and implementation of these guidelines.

The NIH staff will provide educational opportunities for the extramural and intramural community concerning this policy; monitor its implementation during the development, review, award and conduct of research; and manage the NIH research portfolio to address the policy.

1. Principal Investigators

Principal investigators should assess the theoretical and/or scientific linkages between gender, race/ethnicity, and their topic of study. Following this assessment, the principal investigator and the applicant institution will address the policy in each application and proposal, providing the required information on inclusion of women and minorities and their subpopulations in research projects, and any required justifications for exceptions to the policy. Depending on the purpose of the study, NIH recognizes that a single study may not include all minority groups.

2. Institutional Review Boards (IRBs)

As the IRBs implement the guidelines, described herein, for the inclusion of women and minorities and their subpopulations, they must also implement the regulations for the protection of human subjects as described in title 45 CFR part 46, "Protection of Human Subjects." They should take into account the Food and Drug Administration's "Guidelines for the Study and

Evaluation of Gender Differences in the Clinical Evaluation of Drugs," Vol. 58 Federal Register 39406.

3. Peer Review Groups

In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections), technical evaluation groups, and intramural review panels will be instructed, as follows:

- To evaluate the proposed plan for the inclusion of minorities and both genders for appropriate representation or to evaluate the proposed justification when representation is limited or absent,
- To evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects,
- To evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research,
- To determine whether the design of clinical trials is adequate to measure differences when warranted,
- To evaluate the plans for recruitment/outreach for study, participants, and
- To include these criteria as part of the scientific assessment and assigned score.

4. NIH Advisory Councils

In addition to its current responsibilities for review of projects where the peer review groups have raised questions about the appropriate inclusion of women and minorities, the Advisory Council/Board of each Institute/Center shall prepare biennial reports, for inclusion in the overall NIH Director's biennial report, describing the manner in which the Institute/Center has complied with the provisions of the statute.

5. Institute/Center Directors

Institute/Center Directors and their staff shall determine whether: (a) The research involving human subjects, (b) the Phase III clinical trials, and (c) the exclusions meet the requirements of the statute and these guidelines.

6. NIH Director

The NIH Director may approve, on a case-by-case basis, the exclusion of projects, as recommended by the Institute/Center Director, that may be inappropriate to include within the requirements of these guidelines on the basis of circumstances other than the health of the subjects, the purpose of the research, or costs.

7. Recruitment Outreach by Extramural and Intramural Investigators

Investigators and their staff(s) are urged to develop appropriate and culturally sensitive outreach programs and activities commensurate with the goals of the study. The objective should be to actively recruit the most diverse study population consistent with the purposes of the research project. Indeed, the purpose should be to establish a relationship between the investigator(s) and staff(s) and populations and community(ies) of interest such that mutual benefit is derived for participants in the study. Investigator(s) and staff(s) should take precautionary measures to ensure that ethical concerns are clearly noted, such that there is minimal possibility of coercion or undue influence in the incentives or rewards offered in recruiting into or retaining participants in studies. It is also the responsibility of the IRBs to address these ethical concerns.

Furthermore, while the statute focuses on recruitment outreach, NIH staff underscore the need to appropriately retain participants in clinical studies, and thus, the outreach programs and activities should address both recruitment and retention.

To assist investigators and potential study participants, NIH staff have prepared a notebook, "NIH Outreach Notebook on the Inclusion of Women and Minorities in Biomedical and Behavioral Research." The notebook addresses both recruitment and retention of women and minorities in clinical studies, provides relevant references and case studies, and discusses ethical issues. It is not intended as a definitive text on this subject, but should assist investigators in their consideration of an appropriate plan for recruiting and retaining participants in clinical studies. The notebook is expected to be available early in 1994.

8. Educational Outreach by NIH to Inform the Professional Community.

NIH Staff will present the new guidelines to investigators, IRB members, peer review groups, and Advisory Councils in a variety of public educational forums.

9. Applicability to Foreign Research Involving Human Subjects

For foreign awards, the NIH policy on inclusion of women in research conducted outside the U.S. is the same as that for research conducted in the U.S.

However, with regard to the population of the foreign country, the definition of the minority groups may be different than in the U.S. If there is scientific rationale for examining subpopulation group differences within the foreign population, investigators should consider designing their studies to accommodate these differences.

V. Definitions

Throughout the section of the statute pertaining to the inclusion of women and minorities, terms are used which require definition for the purpose of implementing these guidelines. These terms, drawn directly from the statute, are defined below.

A. Clinical Trial

For the purpose of these guidelines, a "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a

standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

B. Research Involving Human Subjects

All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research under this policy. Under this policy, the definition of human subjects in title 45 CFR part 46, the Department of Health and Human Services regulations for the protection of human subjects applies: "Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains: (1) Data through intervention or interaction with the individual, or (2) identifiable private information." These regulations specifically address the protection of human subjects from research risks. It should be noted that there are research areas (Exemptions 1-6) that are exempt from these regulations. However, under these guidelines, NIH-supported biomedical and behavioral research projects involving human subjects which are exempt from the human subjects regulations should still address the inclusion of women and minorities in their study design. Therefore, all biomedical and behavioral research projects involving human subjects will be evaluated for compliance with this policy.

C. Valid Analysis

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- Allocation of study participants of both genders and from different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
- Unbiased evaluation of the outcome(s) of study participants, and
- Use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the gender and racial/ethnic groups.

D. Significant Difference

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

E. Racial and Ethnic Categories

1. Minority Groups

A minority group is a readily identifiable subset of the U.S. population which is distinguished by either racial, ethnic, and/or cultural heritage.

The Office of Management and Budget (OMB) Directive No. 15 defines the minimum standard of basic racial and ethnic categories, which are used below. NIH has chosen to continue the use of these definitions because they allow comparisons to many national data bases, especially national health data bases. Therefore, the racial and ethnic categories described below should be used as basic guidance, cognizant of the distinction based on cultural heritage.

American Indian or Alaskan Native: A person having origins in any of the original peoples of North America, and who maintains cultural identification through tribal affiliation or community recognition.

Asian or Pacific Islander: A person having origins in any of the original peoples of the Far East, Southeast Asia, the Indian subcontinent, or the Pacific Islands. This area includes, for example, China, India, Japan, Korea, the Philippine Islands and Samoa.

Black, not of Hispanic Origin: A person having origins in any of the black racial groups of Africa.

Hispanic: A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race.

2. Majority Group

White, not of Hispanic Origin: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

NIH recognizes the diversity of the U.S. population and that changing demographics are reflected in the changing racial and ethnic composition of the population. The terms "minority groups" and "minority subpopulations" are meant to be inclusive, rather than exclusive, of differing racial and ethnic categories.

3. Subpopulations

Each minority group contains subpopulations which are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific racial and ethnic origin. Attention to subpopulations also applies to individuals of mixed racial and/or ethnic parentage. Researchers should be cognizant of the possibility

that these racial/ethnic combinations may have biomedical and/or cultural implications related to the scientific question under study.

F. Outreach Strategies

These are outreach efforts by investigators and their staff(s) to appropriately recruit and retain populations of interest into research studies. Such efforts should represent a thoughtful and culturally sensitive plan of outreach and generally include involvement of other individuals and organizations relevant to the populations and communities of interest, e.g., family, religious organizations, community leaders and informal gatekeepers, and public and private institutions and organizations. The objective is to establish appropriate lines of communication and cooperation to build mutual trust and cooperation such that both the study and the participants benefit from such collaboration.

G. Research Portfolio

Each Institute and Center at the NIH has its own research portfolio, i.e., its "holdings" in research grants, cooperative agreements, contracts and intramural studies. The Institute or Center evaluates the research awards in its portfolio to identify those areas where there are knowledge gaps or which need special attention to advance the science involved. NIH may consider funding projects to achieve a research portfolio reflecting diverse study populations. With the implementation of this new policy, there will be a need to ensure that sufficient resources are provided within a program to allow for data to be developed for a smooth transition from basic research to Phase III clinical trials that meet the policy requirements.

VI. Discussion—Issues in Scientific Plans and Study Designs

A. Issues in Research Involving Human Subjects

The biomedical and behavioral research process can be viewed as a stepwise process progressing from discovery of new knowledge through research in the laboratory, research involving animals, research involving human subjects, validation of interventions through clinical trials, and broad application to improve the health of the public.

All NIH-supported biomedical and behavioral research involving human subjects is defined broadly in this guidance as clinical research. This is broader than the definition provided in the 1990 NIH Guidance and in many program announcements, requests for applications, and requests for proposals since 1990.

The definition was broadened because of the need to obtain data about minorities and both genders early in the research process when hypotheses are being formulated, baseline data are being collected, and various measurement instruments and intervention strategies are being developed. Broad inclusion at these early stages of research provides valuable information for designing broadly based clinical trials, which are a subset of studies under the broad category of research studies.

The policy on inclusion of minorities and both genders applies to all NIH-supported biomedical and behavioral research involving human subjects so that the maximum information may be obtained to understand the implications of the research findings on the gender or minority group.

Investigators should consider the types of information concerning gender and minority groups which will be required when designing future Phase III clinical trials, and try to obtain it in their earlier stages of research involving human subjects. NIH recognizes that the understanding of health problems and conditions of different U.S. populations may require attention to socioeconomic differences involving occupation, education, and income gradients.

B. Issues in Clinical Trials

The statute requires appropriate representation of subjects of different gender and race/ethnicity in clinical trials so as to provide the opportunity for detecting major qualitative differences (if they exist) among gender and racial/ethnic subgroups and to identify more subtle differences that might, if warranted, be explored in further specifically targeted studies. Other interpretations may not serve as well the health needs of women, minorities, and all other constituencies.

Preparatory to any Phase III clinical trial, certain data are typically obtained. Such data are necessary for the design of an appropriate Phase III trial and include observational clinical study data, basic laboratory (i.e. in vitro and animal) data, and clinical, physiologic, pharmacokinetic, or biochemical data from Phase I and Phase II studies. Genetic studies, behavioral studies, and observational, natural history, and epidemiological studies may also contribute data.

It is essential that data be reviewed from prior studies on a diverse population, that is, in subjects of both genders and from different racial/ethnic groups. These data must be examined to determine if there are significant differences of clinical or public health importance observed between the subgroups.

While data from prior studies relating to possible differences among intervention effects in different subgroups must be reviewed, evidence of this nature is likely to be less convincing than that deriving from the subgroup analyses that can be performed in usual-sized Phase III trials. This is because the evidence from preliminary studies is likely to be of a more indirect nature (e.g. based on surrogate endpoints), deriving from uncontrolled studies (e.g. non-randomized Phase II trials), and based on smaller numbers of subjects than in Phase III secondary analyses. For this reason, it is likely that data from preliminary studies will, in the majority of cases, neither clearly reveal significant differences of clinical or public health importance

between subgroups of patients, nor strongly negate them.

In these cases, Phase III trials should still have appropriate gender and racial/ethnic representation, but they would not need to have the large sample sizes necessary to provide a high statistical power for detecting differences in intervention effects among subgroups. Nevertheless, analyses of subgroup effects must be conducted and comparisons between the subgroups must be made. Depending on the results of these analyses, the results of other relevant research, and the results of meta-analyses of clinical trials, one might initiate subsequent trials to examine more fully these subgroup differences.

C. Issues Concerning Appropriate Gender Representation

The "population at risk" may refer to only one gender where the disease, disorders, or conditions are gender specific. In all other cases, there should be approximately equal numbers of both sexes in studies of populations or subpopulations at risk, unless different proportions are appropriate because of the known prevalance, incidence, morbidity, mortality rates, or expected intervention effect.

D. Issues Concerning Appropriate Representation of Minority Groups and Subpopulations in All Research Involving Human Subjects Including Phase III Clinical Trials

While the inclusion of minority subpopulations in research is a complex and challenging issue, it nonetheless provides the opportunity for researchers to collect data on subpopulations where knowledge gaps exist. Researchers must consider the inclusion of subpopulations in all stages of research design. In meeting this objective, they should be aware of concurrent research that addresses specific subpopulations, and consider potential collaborations which may result in complementary subpopulation data.

At the present time, there are gaps in baseline and other types of data necessary for research involving certain minority groups and/or subpopulations of minority groups. In these areas, it would be appropriate for researchers to obtain such data, including baseline data, by studying a single minority group.

It would also be appropriate for researchers to test survey instruments, recruitment procedures, and other methodologies used in the majority or other population(s) with the objective of assessing their feasibility, applicability, and cultural competence/relevance to a particular minority group or subpopulation. This testing may provide data on the validity of the methodologies across groups. Likewise, if an intervention has been tried in the majority population and not in certain minority groups, it would be appropriate to assess the intervention effect on a single minority group and compare the effect to that obtained in the majority population. These types of studies will advance scientific research and assist in closing knowledge gaps.

A complex issue arises over how broad or narrow the division into different subgroups should be, given the purpose of the research. Division into many racial/ethnic subgroups is tempting in view of the cultural and biological differences that exist among these groups and the possibility that some of these differences may in fact impact in some way upon the scientific question. Alternatively, from a practical perspective, a limit has to be placed on the number of such subgroups that can realistically be studied in detail for each intervention that is researched. The investigator should clearly address the rationale for inclusion or exclusion of subgroups in terms of the purpose of the research. Emphasis should be placed upon inclusion of subpopulations in which the disease manifests itself or the intervention operates in an appreciable different way. Investigators should report the subpopulations included in the study.

An important issue is the appropriate representation of minority groups in research, especially in geographical locations which may have limited numbers of racial/ethnic population groups available for study. The investigator must address this issue in terms of the purpose of the research, and other factors, such as the size of the study, relevant characteristics of the disease, disorder or condition, and the feasibility of making a collaboration or consortium or other arrangements to include minority groups. A justification is required if there is limited representation. Peer reviewers and NIH staff will consider the justification in their evaluations of the project.

NIH interprets the statute in a manner that leads to feasible and real improvements in the representativeness of different racial/ethnic groups in research and places emphasis on research in those subpopulations that are disproportionately affected by certain diseases or disorders.

VII. NIH Contacts for More Information

The following senior extramural staff from the NIH Institutes and Centers may be contacted for further information about the policy and relevant Institute/Center programs:

Dr. Marvin Kalt, National Cancer Institute, 6130 Executive Boulevard, Executive Plaza North, Room 600A, Bethesda, Maryland 20892, Tel: (301) 496-5147.

Dr. Richard Mowery, National Eye Institute, 6120 Executive Boulevard, Executive Plaza South, Room 350, Rockville, Maryland 20892, Tel: (301) 496-5301.

Dr. Lawrence Friedman, National Heart, Lung and Blood Institute, 7550 Wisconsin Avenue, Federal Building, Room 212, Bethesda, Maryland 20892, Tel: (301) 496-2533.

Dr. Miriam Kelty, National Institute on Aging, 7201 Wisconsin Avenue, Gateway Building, Room 2C218, Bethesda, Maryland 20892, Tel: (301) 496-9322.

Dr. Cherry Lowman, National Institute on Alcohol Abuse and Alcoholism, 6000 Executive Boulevard, Rockville, Maryland 20892, Tel: (301) 443-0796.

Dr. George Counts, National Institute of Allergy and Infectious Diseases, 6003 Executive Boulevard, Solar Building, Room 207P, Bethesda, Maryland 20892, Tel: (301) 496-8214.

Dr. Michael Lockshin, National Institute of Arthritis and Musculoskeletal and Skin Diseases, 9000 Rockville Pike, Building 31, Room 4C32, Bethesda, Maryland 20892, Tel: (301) 496-0802.

Ms. Hildegard Topper, Bethesda, National Institute of Child Health and Human Development, 9000 Rockville Pike, Building 31, Room 2A-03, Bethesda, Maryland 20892, Tel: (301) 496-0104.

Dr. Earleen Elkins, National Institute of Deafness and Other Communication Disorders, 6120 Executive Boulevard, Executive Plaza South, Room 400, Rockville, Maryland 20892, Tel: (301) 496-8683.

Dr. Norman S. Braveman, National Institute on Dental Research, 5333 Westbard Avenue, Westwood Building, Room 509, Bethesda, Maryland 20892, Tel: (301) 594-7648.

Dr. Walter Stolz, National Institute of Diabetes and Digestive and Kidney Diseases, 5333 Westbard Avenue, Westwood Building, Room 657, Bethesda, Maryland 20892, Tel: (301) 594-7527.

Ms. Eleanor Friedenberg, National Institute on Drug Abuse, 5600 Fishers Lane, Parklawn Building, Room 10-42, Rockville, Maryland 20857, Tel: (301) 434-2755.

Dr. Gwen Collman, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, North Carolina 27709, Tel: (919) 541-4980.

Dr. Lee Van Lenten, National Institute of General Medical Sciences, 5333 Westbard Avenue, Westwood Building, Room 905, Bethesda, Maryland 20892, Tel: (301) 594-7744.

Dr. Dolores Parron, National Institute of Mental Health, 5600 Fishers Lane, Parklawn Building, Room 17C-14, Rockville, Maryland 20857, Tel: (301) 443-2847.

Dr. Constance Atwell, National Institute of Neurological Disorders and Stroke, 7550 Wisconsin Ave., Federal Building, Room 1016, Bethesda, Maryland 20892, Tel: (301) 496-9248.

Dr. Mark Guyer, National Center for Human Genome Research, 9000 Rockville Pike, Building 38A, Room 605, Bethesda, Maryland 20892, Tel: (301) 496-0844.

Dr. Teresa Radebaugh, National Center for Nursing Research, 5333 Westbard Avenue, Westwood Building, Room 754, Bethesda, Maryland 20892, Tel: (301) 594-7590.

Dr. Harriet Gordon, National Center for Research Resources, 5333 Westbard Avenue, Westwood Building, Room 10A03, Bethesda, Maryland 20892, Tel: (301) 594-7945.

Dr. David Wolff, Fogarty International Center, 9000 Rockville Pike, Building 31, Room B2C39, Bethesda, Maryland 20892, Tel: (301) 496-1653.

Dated: March 3, 1994.

Harold Varmus,

Director, NIH.

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Appendix B

Questions and Answers

Concerning the 1994 NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research

National Institutes of Health

PREFACE

As required by the National Institutes of Health (NIH) Revitalization Act of 1993, the NIH published **Guidelines on the Inclusion of Women and Minorities As Subjects in Clinical Research** in the *Federal Register* of March 28, 1994, (59 FR 14508-14513) and in the NIH *Guide for Grants and Contracts* of March 18, 1994. Research applications and proposals to be supported by NIH must comply with this policy as mandated by law.

This document contains a series of questions and answers to assist in the preparation of research applications and proposals in accordance with the 1994 NIH Guidelines. The questions cover many areas and are listed in a table of contents for ease in finding specific topics of interest. Although this document provides additional clarification and explanation, it is important to read the NIH Guidelines.

If there are questions about this policy, please contact the NIH representative from the appropriate Institute, Center or Division on the following pages (Question 36). This document will be updated as necessary should there be any significant changes in the NIH Guidelines as a result of comments received during the first year of implementation of the Guidelines.

This document is available electronically on the NIH Gopher (gopher.nih.gov 70) under 'From the Office of Extramural Research' and on the NIH Grantline (data line 301-402-2221; Dr. John James, moderator, 301-594-7270; jqj@cu.nih.gov). For additional information about online sources of documents about the extramural research programs of the NIH, refer to the NIH *Guide for Grants and Contracts*, Volume 23, Issue 23, June 17, 1994, or email questions to q2c@cu.nih.gov.

Note: This document replaces Appendix 5 of NIH Instruction and Information Memorandum OER 90-5.

CONTENTS

E. AWARDS

QUESTIONS AND ANSWERS CONCERNING THE 1993 NIH GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH

A. POLICY

1. **What does the new policy say?**

It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an Institute/Center Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

NIH funding components will not award any grant, cooperative agreement or contract or support any intramural project, to be conducted or funded in Fiscal Year 1995 and thereafter, that does not comply with this policy.

(See Sections III.A. and III.C. in the NIH Guidelines)

2. **What are the major differences between the 1990 policy and the Guidelines required by the 1993 NIH Revitalization Act?**

In addition to continuing the 1990 requirement to include women and minority groups in clinical research, the new Guidelines:

- broaden the definition of clinical research to include all research involving human subjects;

- direct that members of minority subpopulations be included in all human subject research;

- require inclusion of women and minorities and their subpopulations in Phase III clinical trials such that valid analyses of differences in intervention effect can be accomplished;

- promote development of outreach programs to recruit women and minorities and their subpopulations into clinical studies; and

- do not allow cost as an acceptable reason for excluding these groups in clinical trials.

(See Section I. in the NIH Guidelines)

3. **What is the scientific basis of the policy?**

The guidelines and policy are *science driven* so that maximum information may be obtained to understand the implications of the research findings on the gender or minority group. As defined in Webster's dictionary, science is "systematized knowledge derived from observation, study and experimentation carried on in order to determine the nature or principles of what is being studied."

There is a need to obtain this systematized knowledge and data about minorities and both genders early in the research process when hypotheses are being formulated, baseline data are being collected, and various measurement instruments and intervention strategies are being developed. Broad inclusion at these early stages of research provides valuable information for informed decisions in designing subsequent broadly based Phase III clinical trials.

Research is a continuum of studies from basic laboratory to observational to clinical. Assessment of differential effects of an intervention or therapy on women, men, or members of minority groups and their subpopulations requires fundamental information on such groups. Therefore, at the earliest stages of research, investigators are encouraged to include individuals or tissues of both genders and diverse racial and ethnic groups in order to generate information necessary for the rational design of appropriate Phase III clinical trials. Investigators are encouraged to report results on gender and minority groups and their subpopulations, as appropriate.

Thus, this policy should result in a variety of new research opportunities to address significant gaps in knowledge about health problems that affect women and racial/ethnic minorities and their subpopulations.

(See Section VI.A. in the NIH Guidelines)

4. **Who is responsible for implementation of the Guidelines?**

The entire scientific community has a responsibility for implementing the policy as a partnership between research subjects, principal investigators, institutional review boards, peer review groups, NIH staff, NIH advisory councils, NIH Institute and Center Directors, and the NIH Director in fulfilling the intent of the law and ensuring that the results of research are broadly applicable to the entire population.

Principal investigators should assess the theoretical and/or scientific linkages between gender, race/ethnicity, and their topic of study in preparing their applications and conducting their research. Institutional review boards (IRBs) should review NIH protocols in terms of the NIH inclusion policy during their review for protection of human subjects. Peer review groups will include a scientific and technical merit evaluation of the proposed inclusion plan and assign appropriate scores. The Advisory Council/Board of each Institute/Center will prepare biennial reports describing the manner in which the Institute/Center has complied with the provisions of the statute.

The NIH staff will provide educational opportunities for the extramural and intramural community concerning this policy; monitor its implementation during the development, review, award and conduct of research; and manage the NIH research portfolio to address the policy. Research subjects will be involved as voluntary participants in NIH-supported research.

(See Section IV.C. in the NIH Guidelines)

5. **What is meant by minority groups and minority subpopulations?**

The following four racial/ethnic minority groups are those identified by the Office of Management and Budget for federal reporting: American Indian/Alaskan Native; Asian/Pacific Islander; Black, not of Hispanic Origin; and Hispanic. Caucasians, not of Hispanic Origin, are considered a majority group for the purposes of this policy. The classification of an individual is by self identification. This classification is for administrative purposes and is prevalent in the scientific and other literature and databases available for research. Data may be collected on subpopulations and persons of mixed race/ethnicity, but must be aggregated into these groups for reporting purposes to NIH. The OMB is currently evaluating whether there should be any modifications to these categories.

For scientific purposes, it may be necessary to deal with the very real biological and cultural differences that exist not only among these broad racial/ethnic groupings, but also within the groups because of their differing languages, cultural traditions, and biological characteristics; thus, variability is to be expected within the Asian or Pacific Island populations, the various American Indian tribes, groups of various Hispanic origins, etc.

In its Guidelines, NIH has defined a minority group as " . . . a readily identifiable subset of the U.S. population which is distinguished by either racial, ethnic, and/or cultural heritage." Each minority group contains subpopulations that may be defined for geographic origin, national origin, cultural differences, or mixed racial and/or ethnic parentage. The minority group or subpopulation to which an individual belongs is determined by self-reporting. For illustrative purposes, several major subpopulations for each United States (U.S.) minority group are listed below, although other examples of subpopulations may be used by investigators for their research projects:

- **American Indians/Alaskan Native**
  American Indian, specify tribe
  Alaskan Eskimo
  Aleut

- **Asian/Pacific Islander**
  Chinese
  Filipino
  Japanese
  Asian Indian
  Korean
  Vietnamese

- **Black, not of Hispanic Origin**
  Caribbean Black
  African

- **Hispanic**
  Mexican
  Puerto Rican
  Cuban
  Other specific Central and South American origin
  (OMB does not include Iberian peninsula natives as Hispanic.)

The NIH reporting requirements (see Question 34) also allow for those cases when the racial/ethnic group is "Other or Unknown."

The purpose of investigators routinely specifying the racial ethnic population(s) under investigation is to begin to systematically obtain data on the various minority groups and subpopulations to fill the gaps of health research information on those populations so that the study results may be optimally applicable to all citizens. Investigators may report their findings in the research literature consistent with the purpose of the research.

(See Section V.E.1. through V.E.3. in the NIH Guidelines)

6. **What is the NIH definition of clinical research?**

All research involving human subjects is considered clinical research for the purposes of this NIH policy. This includes both biomedical and behavioral research. Small scale, exploratory, or observational studies fall under this policy as well as large scale studies.

The policy is based on the definition in Federal regulations for human subjects: "...living individual(s) about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information." [45 CFR 46.102(f)] However, research exempted from human subjects protection regulations as defined by 45 CFR 46.101(b) is not exempted from NIH policies on inclusion of both genders and of minorities in study populations and must be evaluated and coded. Thus, the inclusion covers individuals or tissues of both genders and diverse racial and ethnic groups.

The policy extends to all research involving the use of human organs, tissues, and body fluids from living individuals as well as to graphic, written, or recorded information derived from living individuals. Although the use of autopsy material or other material from deceased individuals is not specifically covered by the policy, the appropriate inclusion of both genders and minorities may still be relevant for scientific reasons indicated by the investigator or peer review group.

(See Section V.B. and VI.A. in the NIH Guidelines)

7. **What is the NIH definition of a clinical trial?**

NIH has developed a special definition for clinical trials as used in this policy to distinguish these trials from the other types of clinical research that NIH supports, and from other definitions, e.g., by the Food and Drug Administration (FDA). These clinical trials are an important subset of all clinical research projects.

For the purposes of the NIH policy, a clinical trial is a broadly based prospective Phase III clinical investigation that is designed to evaluate an experimental intervention in comparison with a standard or control intervention or to compare two or more existing treatments. Often the aim of such investigations is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacological, nonpharmacological, and behavioral interventions given for disease prevention, prophylaxis, diagnosis or therapy. Community trials and other population-based intervention trials are also included.

Discussion

The NIH definition of a clinical trial is broad and includes the wide range of research that NIH sponsors. It differs from the FDA definition of Phase III clinical trials, which focuses primarily on clinical investigation of drugs, vaccines, biologics, and devices. The FDA defines Phase I, II, and

III trials (21 CFR Section 312.21, 4-1-94 edition) as follows: "Phase 3 studies are expanded, controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects."

In determining whether a study fits the NIH definition of a clinical trial, an essential consideration is trial outcome—whether it would contribute to a change in the standard of care or contribute to a change in public health policy, regardless of the number of participants in the study.

(See Section V.A. in the NIH Guidelines)

8. **Are there special requirements for NIH-defined clinical trials?**

YES. Applications for NIH-defined Phase III clinical trials must include a review of the available evidence to show whether or not clinically important gender or race/ethnicity differences in the response to the intervention are to be expected. The design of such trials must reflect the current state of knowledge about any such expected differences.

Evidence may include, but is not limited to, data from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacologic studies, and observational, natural history, epidemiologic, and other relevant studies. The nature of the evidence should be used to determine the extent to which women, men, and members of minority groups and their subpopulations must be included.

Three kinds of circumstances are described in the NIH Guidelines, based on the findings of the review of the prior data; in these cases, the terms "significant" and "valid analysis" are defined and used in a way that is different from the usual convention for clinical trials:

- If the data strongly indicate the existence of significant differences of clinical or public health importance in intervention effect among subgroups, the primary question(s) to be addressed by the trial must be designed for valid analysis, with high statistical power, of the intervention effect in the separate genders and/or minorities or their subpopulations that are hypothesized to be different. For example, if men and women are thought to respond differently to an intervention, then the Phase III trial must be designed to answer two separate primary questions, one for men and the other for women, with adequate sample size for each.

- If the data strongly support no significant difference of clinical or public health importance in intervention effect between subgroups, then the trial is designed to measure the primary question of intervention effect; gender or race/ethnicity will not be required as subject selection criteria. However, the inclusion of gender or racial/ethnic subgroups is still strongly encouraged.

- If the data are inconclusive about potential differences, then the trial will be required to include sufficient and appropriate recruitment of gender and racial/ethnic subgroups, so that valid analysis of the intervention effect in subgroups can be performed. However, the trial will not be required to provide high statistical power for each subgroup. It should be recognized that the results of these types of subgroup analyses often provide the basis for doing additional studies to more fully examine subgroup differences. Existing data on the disease, disorder, or conditions under study should be used to guide the design of study populations for NIH-defined clinical trials. When these NIH-defined clinical trials are being designed, consideration should be given to using national statistics on the disease, disorder, or condition under study, as well as national population and subpopulation statistics.

(See Sections III.B. and VI.B. in the NIH Guidelines)

9. **What do we mean by valid analysis?**

The term "valid analysis" is defined in this policy as an unbiased assessment. Valid analysis can and should be conducted for both small and large Phase III clinical studies. A valid analysis does not necessarily need a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- allocation of study participants of both genders and from different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,

- unbiased evaluation of the outcome(s) of study participants, and

- use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the gender and racial/ethnic groups.

(See Section V.C. in the NIH Guidelines)

10. **Is there a summary table to distinguish the inclusion requirements between clinical research and clinical trials?**

This table summarizes the inclusion requirements for clinical research on human subjects and for clinical trials.

	Include Women and Minorities	Include Minority Subpopulations	Required to Measure Differences
Clinical Research	✓	✓	—
Clinical Trials	✓	✓	✓

All studies involving human subjects must include women and minorities and minority subpopulations, subject to the justifications and exclusions noted previously.

Phase III clinical trials are, in addition, required to provide valid analyses to measure differences of clinical or public health importance in intervention effects based on gender or racial/ethnic subgroups when there is evidence supporting differences.

Note that Phase I and Phase II clinical trials, and many small studies, are included under "research involving human subjects" or "human studies" and are not required to be designed to measure differences of intervention effects. For such studies, the systematic inclusion and reporting of information on women and minorities will contribute to an increase in the scientific base of knowledge about them.
(See Sections III.A and B. in the NIH Guidelines)

11. **Is there a decision tree available to help clarify the policy?**

A "Decision Tree for Inclusion of Women and Minorities in Clinical Research" is available as a series of questions and instructions and as a graphic representation.
(See Page 4)

B. Applications

12. **What information should applicants provide when justifying their choice of subjects in a clinical study?**

In addition to the usual information provided in a research application or proposal, applicants for clinical studies should discuss the following issues relevant to this policy:

- *Disease/disorder/condition characteristics*—Does the disease, disorder, or condition affect men and women, and racial/ethnic groups differently than the majority? Describe and provide known data, including references.

- *Treatment or intervention characteristics*—Do clinically important gender or racial/ethnic differences exist in the intervention effect? Describe and provide known data, including references.

This information will be especially important in determining whether the proposed study will be appropriately considered as an NIH-defined clinical trial, and whether the study design should evaluate different intervention effects by gender, race, and/or ethnicity.

(See Question 8 and Section IV.C.1. in the NIH Guidelines)

13. **What factors should be considered in determining inclusion of women and minorities and their subpopulations?**

In deciding to what extent women and minorities should be included in a study and, thus, what outreach efforts are necessary, it is essential that the investigator carefully review the scientific question or hypothesis proposed. The need for incorporation of women and minority subpopulations will derive from the scientific question. As such, the investigator should consider the following:

- Is the scientific question or hypothesis applicable equally to both genders and to all minority groups and their subpopulations?

- Is the condition under study more prevalent or severe in one particular group?

- Have sufficient studies already been performed in one or more groups, leaving gaps that can be filled by focusing the research on certain population groups?

Having considered these questions, the investigator should then ask:

- Can the need for appropriate diversity be met by obtaining access to participants from a single clinic or facility? Will oversampling of certain groups be possible?

- If a single clinic or facility is not adequate, can the needed participants be enrolled by going to hospitals or other clinical facilities in the nearby geographic region?

- If demographic limitations preclude answering scientific questions locally for the appropriate gender and minority groups, is it feasible or necessary to expand the geographic area or to establish satellite centers?

(See Question 11 and Section VI.D. in the NIH Guidelines)

14. **What type of information is required in describing the diversity of the composition of the study population?**

As stated in the policy: "The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The research plan should describe the proposed study population in terms of gender and racial/ethnic composition, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants." (III.A.)

The grant application instructions (PHS 398) require this information in the Research Design and Methods section. The format for reporting is shown in Question 34. In addition, the "Human Subjects" section of the PHS 398 also requires applicants to do the following:

- Describe the characteristics of the subject population, including their anticipated number, age range, and health status. Identify the criteria for inclusion or exclusion of any subpopulation.

- Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.

❧ Describe plans for the recruitment of subjects and the consent procedures to be followed.

The plans for recruitment and retention of study participants should be clearly presented in terms of the methods and mechanisms for outreach. Initial Review Group members look for various types of evidence that the investigator has addressed the inclusion of both women and men, and minorities and their subpopulations, in a satisfactory manner. Such evidence may include (but is not limited to), information on the population characteristics of the disease or condition under study; national and local demographics of the population; knowledge and understanding of the racial/ethnic/cultural characteristics of the population; prior experience and collaborations in recruitment and retention of the populations and subpopulations to be studied; and the plans, arrangements and letters of commitment from relevant community groups and organizations for the planned study. Justifications should also be made in support of appropriate staffing needs for outreach plans. Exclusion of any group should be based on scientific considerations, and not simply for the convenience of the investigator. For single hospital, clinic, and university studies, it is important to present data on the characteristics of the population served by the site compared to the broader community or regional population. Planned enrollment should be viewed in terms of the demographics of the disease or condition, rather than local demographics or referral pattern, in order to avoid selection bias. For multi-center trials, the combined enrollment from all recruitment sites may achieve the required gender and racial/ethnic composition for the study. Study designs involving oversampling may also be appropriately justified. See Question 30 for a further discussion of contract projects.

(See Section III.A. and IV.C.1. and C.3. in the NIH Guidelines)

15. **Do all minority groups and subpopulations have to be included in each study population?**

Investigators should decide which minority groups and subpopulations will be included in the study based on the scientific question under study. It is not expected that every minority group and subpopulation will be included in each study. Broad representation and diversity are strongly encouraged, even if multiple clinics and sites are needed to accomplish it. When determining the composition of the study population, scientific issues (e.g., high prevalence of a disease/condition in certain minority groups, health of the subjects, different disease characteristics, or gap(s) in knowledge in a minority subpopulation) should be considered. For smaller studies, investigators should discuss the proposed study population and provide a justification for the specific minority groups available, including those absent or in limited numbers.

(See Section II. [subsection on exclusions] and IV.C.1. in the NIH Guidelines)

16. **Does the policy permit a study population that contains only one gender or minority group or subpopulation?**

YES. If a study of only one gender or minority group or subpopulation is proposed, there must be a scientific justification for limiting the diversity of the study population, such as high prevalence of the condition, unique disease characteristics, or gaps in knowledge in the selected population. The review committee will include the adequacy and scientific appropriateness of the proposed study population, and any justification, among the criteria used in its determination of the priority score. Women of childbearing potential should not be routinely excluded from participation in clinical research.

(See Sections IV.C.3., VI.C. and VI.D. in the NIH Guidelines)

17. **What should applicants do if they are in a geographic area that does not offer a study population with the diversity required by the policy?**

Investigators based in areas of the country where the population is primarily majority, or of one racial/ethnic group, will have difficulty recruiting sufficient numbers of participants to represent all of the racial/ethnic groups that may be significantly affected by the condition, disorder, or disease of interest. Can geographic considerations justify limited representation? This question has been asked by investigators from several states (e.g., Vermont, New Hampshire, Iowa, Minnesota). If geography is the only basis for lack of representation, it cannot be used to justify limited representation.

Investigators have long been required by NIH to be inclusive in their study populations. The new guidelines expand on those previously in place. Applicants/offerors must select study participants in terms of the purpose of the research and other factors, such as prior research findings, the size of the study, relevant characteristics of and gaps in knowledge about the disease, disorder, or condition, and the feasibility of developing a collaboration or consortium or other arrangements to include minority groups.

Each investigator is given the opportunity to provide a clear and compelling description and rationale for the proposed study population and its appropriateness for the purpose of the research. When there is limited representation, the investigator must provide a justification satisfactory to the Institute or Center Director, based on the health of the participants and the scientific needs of the research being proposed.

The meaning of "adequate representation" is tied to the purpose of the research. It does not necessarily mean that all groups are to be included, nor does it mean that there must be sufficient numbers for separate analysis. For example, small, exploratory studies are not expected to have representation from all racial/ethnic groups. Single gender or minority subgroup studies

are possible. However, Phase III trials, where gender, race or ethnic background can be a factor, must be inclusive and diverse and address racial/ethnic subgroup differences because these trials have broad societal impact on behavior or therapeutic interventions or standard of care.

When an investigator is aware of similar research completed or underway employing populations complementary to those available in his/her locale, this can be presented as a rationale for limited representation.

In other cases, if the appropriate participants are not available in the locale of the applicant institution, investigators are encouraged to seek collaborators in other geographic areas. Plans should be presented to recruit outside that area either by the investigator or through collaborative arrangements with investigators who do have access to more diverse populations. Particularly when multi-center clinical trials are proposed, the inclusion requirements may be met by combining recruitment from the multiple sites; in these trials, each clinical site must still describe its planned recruitment, and will be evaluated on that basis.

When adequate representation is not provided and is not adequately justified, it should have substantial negative impact on the evaluation of merit of an application. The NIH program staff is available to work with investigators whose study site(s) may not have adequate gender or minority representation (see Question 36).

Peer reviewers will consider the proposed study and any justifications provided for the applicant's choice of study population(s) using the required review criteria and their scientific judgment, as discussed below. When peer reviewers have identified concerns, NIH staff will work with investigators to resolve the concerns before any award is made. Furthermore, if an NIH Institute or Center chooses to fund a Phase III clinical study that is inconsistent with the Guidelines, it is the responsibility of the Institute or Center to either take administrative action to revise the pending trial or initiate complementary activity to address the gender or minority concern.

These Guidelines are in no way intended to discriminate against areas that do not have diverse populations, nor do we believe that they will have that effect. The NIH commitment is to ensure that medical knowledge from NIH research benefits the entire population.

(See Sections IV.C.3., V.G., and VI.D. in the NIH Guidelines)

18. **Can study populations in other selected studies be used to justify a study population that does not include both men and women or racial/ethnic minority groups?**

Investigators may propose that the planned study population composition has limited gender and/or minority representation, and is justified because the combination of the study population in their application and related past or ongoing studies provide the diversity required by the policy. Applicants should use published reports and discussions with NIH staff concerning ongoing research to identify studies that provide the appropriate diversity. In some cases, duplication of comparable data that include the excepted gender or population group may not be necessary.

(See Sections V.G. and III.A. in the NIH Guidelines)

19. **What is meant by outreach efforts to recruit and retain women and minorities in studies?**

Outreach efforts are attempts by investigators and their staff to recruit and retain women and minority populations in their studies. Such efforts could include involvement of organizations and persons relevant to the populations and communities of interest (e.g., religious organizations, community leaders, and public and private institutions) in order to develop appropriate and culturally sensitive outreach programs and activities for recruitment and retention of the most diverse study population, consistent with the purposes of the research project.

The research plan should contain a description of the proposed outreach programs for recruiting and retaining women and minorities as participants. Investigators should take precautionary measures to ensure that there is minimal possibility of coercion or undue influence in the incentives or rewards offered to prospective participants when recruiting or attempting to retain participants in studies.

The likelihood of success of the outreach plan will be evaluated as part of the peer review. Typically, peer reviewers use past experience and success as an indicator of an investigator's ability to mount and implement a successful outreach plan.

To assist investigators and potential study participants, NIH staff prepared this notebook, **Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research**. It is not intended as a definitive text on this subject, but should assist investigators in their consideration of an appropriate plan for recruiting and retaining participants in clinical studies. The Office of Research on Women's Health also published *Recruitment and Retention of Women in Clinical Studies*, a report from a 1993 workshop identifying barriers for including women in clinical studies and providing recommendations to overcome these barriers.

(See Section IV.C.7. and V.F. in the NIH Guidelines)

20. **In multi-center clinical studies, must each study site meet the inclusion requirements separately?**

Each study site must describe its planned recruitment, retention and outreach plans, which will be evaluated as part of the initial review of the application.

The recruitment goals for women, men, and minorities may vary at different sites in multi-center clinical studies; however, the overall recruitment goals for the study may be met by combining recruitment from all sites. This could be acceptable if the women and minorities populations from the contributing centers do not have some relevant unique characteristics, other than being from those centers, that could limit the value of the study results. As part of its funding plan, the NIH may select recruitment sites with high minority enrollments for inclusion in multi-center studies to achieve inclusion of the most diverse study population. Annual reports on enrollment will be required for each site as well as for the overall study.

(See Section VI.B. in the NIH Guidelines)

21. **Is increased cost an acceptable justification for not including women, minorities, and minority subpopulations in clinical trials?**

NO. The legislation states unequivocally that the cost associated with increasing the diversity of a study population composition to include both women and men, minorities, and minority subpopulations is not an acceptable justification for excluding them from clinical trials. In other types of clinical research, cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources.

(See Section I., II., III.A., and III.B. in the NIH Guidelines)

22. **Is it acceptable to use existing cohorts that are deficient in women or minority participants?**

Competitive continuation (type 2) applications or proposals that propose to complete a study or analyses of existing data bases are exempt from the new policy if they were initiated before June 1993. However, in new (type 1) applications or proposals, use of an existing cohort that lacks the diversity required by the new policy must be justified. The nature of the scientific question, a requirement for data provided by the cohort, or research portfolio balance may provide the basis of a justification. An NIH Institute or Center may also pursue other means of filling programmatic gaps due to the limitations of prior studies in meeting the new policy requirements.

(See Section IV.C.1., V.B., VI.A. and VI.B. in the NIH Guidelines)

C. EXCLUSIONS/JUSTIFICATIONS

23. **What are the circumstances under which it is not necessary to include both women and men, and minorities?**

The law allows for three circumstances. The requirements shall not apply when the inclusion of women and members of minority groups:

1. is inappropriate with respect to the health of the subjects;

2. is inappropriate with respect to the purpose of the research; or

3. is inappropriate under such other circumstances as the Director of NIH may designate.

The NIH Guidelines require a justification, to the satisfaction of an Institute/Center Director, when inclusion of both genders and minorities is not proposed for reasons (1) and (2) above.

(See Sections II. and III.A. in the NIH Guidelines)

24. **What kinds of justifications are acceptable for not including adequate representation of women or men?**

Depending on the specific research questions and design, one or more of the following possible acceptable justifications could apply:

- One gender (male or female) is excluded from the study because:

  – inclusion of these individuals would be inappropriate with respect to their health (e.g., experimental procedures/treatment present unacceptable risk for women of childbearing potential. It should be noted, however, that women of childbearing potential should not be routinely excluded.);

  – the research question addressed is relevant to only one gender; or

  – evidence from prior research strongly demonstrates no difference between genders; or

  – sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.

❧ One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens.)

❧ Gender representation of specimens or existing datasets cannot be accurately determined, (e.g., pooled blood samples, stored specimens, or datasets with incomplete gender documentation are used) and this does not compromise the scientific objectives of the research.

❧ The scientific question requires the use of the same or a comparable study population as that used in an earlier study and the potential gain in scientific knowledge outweighs the imbalance in the study population.

❧ Research is proposed with a pre-defined unique but underrepresented population (e.g., an extensive registry of patients with the condition of interest) and would not be feasible if a different sample were used.

Each of these justifications would be evaluated by Initial Review Groups in the context of the specific scientific goals and issues being addressed. Depending on the details, these justifications may or may not be considered adequate and compelling.

(See Section III.A. and VI.C. in the NIH Guidelines)

25. **What kinds of justification are acceptable for not including adequate representation of all racial/ethnic minorities and subpopulations?**

It is not anticipated that every study will include all minority groups and subgroups. The inclusion of minority groups should be determined by the scientific questions under examination and their relevance to racial/ethnic groups. Applications should describe the subgroups that will be included in the research. The investigator should address inclusion issues in terms of the size of the study, the relevant characteristics of the disease, disorder, condition, or phenomena under study, or the feasibility of making a collaboration or consortium or other arrangements to include representation.

Depending on the specific research questions and design, one or more of the following possible acceptable justifications could apply:

- Some or all minority groups or subgroups are excluded from the study because:

  – inclusion of these individuals would be inappropriate with respect to their health; or

  – the research question addressed is relevant to only one racial/ethnic group; or

  – evidence from prior research strongly demonstrates no differences between racial/ethnic groups on the outcome variables; or

  – a single minority group study is proposed to fill a research gap; or

  – sufficient data already exist with regard to the outcome of comparable studies in the excluded racial/ethnic group(s) and duplication is not needed in this study.

- Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, AND the investigator has satisfactorily addressed this issue in terms of the size of the study, the relevant characteristics of the disease, disorder, or condition, or the feasibility of making a collaboration or consortium or other arrangements to include representation.

- Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race/ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).

- Racial/ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or datasets with incomplete racial/ethnic documentation are used), but this does not compromise the scientific objectives of the research.

Each of these justifications would be evaluated by Initial Review Groups in the context of the specific scientific goals and issues being addressed. Depending on the details, these justifications may or may not be considered adequate and compelling.

(See Section III.A. and VI.D. in the NIH Guidelines)

D. Peer Review

26. **This policy appears to be based on political considerations. Why is it to be reviewed as a part of the science by the Initial Review Groups?**

The policy, while responsive to a Congressional mandate, has a scientific basis, as discussed in Question 3. In clinical research, the endpoint is to gain knowledge that will contribute to the health of the American public. To achieve this goal, research findings must be applicable generally to all of the people who may become or are affected by the conditions, disorders, or diseases that are the focus of the NIH research effort.

The scientific and technical merit of a research project depends, in part, on the appropriateness of the study population for the aims of the research. For example, if a clinical research study population does not include both men and women, the question must be asked: will the results be valid and useful to both men and women? If not, the scientific merit of the study may be diminished. In some circumstances, however, the assessment of scientific merit may not be affected by a more limited representation.

(See Sections V.A. and V.D. in the NIH Guidelines)

27. **How will peer reviewers evaluate applications for compliance with this policy?**

During initial review, peer reviewers will evaluate each project separately in terms of gender and minority representation and determine whether it is scientifically acceptable in regard to the inclusion policy. Their decision will be based on the proposed plans, any justifications provided, and the review criteria noted below. (See Question 30 for a further discussion of contract projects.)

For scientifically acceptable applications, gender representation proposed in the project may include both genders, only females, only males, or unknown gender. Minority representation proposed in the project may include both minority and non-minority subjects, only minority subjects, only non-minority subjects, or unknown minority representation in the subject population. Clinical trials will have additional criteria as discussed previously under Question 8. The quality of the inclusion plans will be factored into the priority score assigned by reviewers.

An application is judged to be unacceptable if it: fails to conform to NIH policy guidelines in relation to the scientific purpose and type of study; or fails to provide sufficient information; or does not adequately justify limited or lack of representation of one gender or minority groups;

or does not realistically address recruitment and retention. The unacceptable inclusion plans should be reflected in a poorer priority score assigned by reviewers if the project is scored. (This "unacceptable" code constitutes a bar to funding unless or until resolved by NIH staff.)

Peer reviewers will be asked to evaluate whether the research plan in the application conforms to these policies, using questions such as the following:

- Is the proposed representation of women and men, and minorities and their subpopulations described?

- Is the proposed representation adequate with respect to the scientific questions under study?

- Have the subpopulations been appropriately identified and reported?

- Are the efforts being made to recruit and retain women and men, and minorities and their subpopulations adequately described and likely to accomplish the goals?

For a Phase III clinical trial: Has evidence been adequately evaluated in terms of whether clinically important gender or racial/ethnic differences in the intervention effect are to be expected? Has the planned trial been designed to take into account the inclusion requirements for the three options previously discussed under Question 8, including the need for valid analysis of the intervention effect in subgroups? Are sufficient numbers of men and women and minorities included to accomplish the valid analysis of differences of intervention effects?

If the proposed representation of women or minorities and their subpopulations is judged as unacceptable, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

Review Criteria

In conducting peer review for scientific and technical merit, appropriately constituted initial review groups (including study sections), technical evaluation groups, and intramural review panels will be instructed to consider the following elements in the recruitment and retention of women and minorities in clinical research.

- Evaluate the proposed plan for the inclusion of women and minorities and their subpopulations for appropriate representation or to evaluate the proposed justification when representation is limited or absent.

❧ Evaluate the proposed exclusion of women and minorities and their subpopulations on the basis that a requirement for inclusion is inappropriate with respect to the health of the subjects.

❧ Evaluate the proposed exclusion of minorities and women on the basis that a requirement for inclusion is inappropriate with respect to the purpose of the research.

❧ Determine whether the design of the study or clinical trial is adequate to measure differences when warranted.

❧ Evaluate the outreach plans for recruitment and retention of study participants.

These criteria, which apply to the full range of NIH-supported clinical research, will form part of the scientific assessment and assigned score.

Reviewers will assign codes, which correspond to the scientific and technical evaluation of the inclusion policy, to scored applications. The codes will be included in summary statements.

Note: Scientific Review Administrators of the Initial Review Groups (IRGs) will treat the evaluation of the representation of women and minorities and their subpopulations in a manner consistent with the evaluation of all other factors that contribute to the overall priority score. The Scientific Review Administrators will not routinely request written clarification from the applicant when the application does not describe and justify the gender or minority composition of the study population. If such information is not contained within the application, and it is not provided prior to the review meeting, the application will be reviewed by the IRG as submitted and the deficiencies will be reflected in the priority score. This procedure is consistent with review of all other parts of the application that contribute to the overall priority score.

(See Section IV.C.3. in the NIH Guidelines)

28. **The policy on inclusion of women and minorities is applied to research projects, rather than applications or proposals. How is this dealt with in the IRG coding?**

The clinical research project is the basic unit requiring compliance with the policy and it is characterized as a research activity focused on a particular problem, with a specific experimental design or protocol, and a particular study population. All research involving human subjects must be reviewed by an Institutional Review Board (IRB). Typically, an IRB examines each research activity involving a particular use of human subjects. Similarly, as a part of the NIH review, each such project will be reviewed and coded by the initial review group (IRG) for appropriate inclusion of both genders and minorities.

An application or proposal may consist of a single project (in which case it would be assigned the same codes as that project), or multiple projects. In addition to codes for each project, applications should be given an overall set of codes reflecting an evaluation of all of the activities being proposed, as indicated in the coding guidelines. In some cases, a series of related studies may involve varying one or more parameter(s) of interest with the same subject population, (e.g., dose-response studies or visual perception studies). Based on its merits and the IRG's judgment, such a series may be considered a single project or multiple projects and coded either as one or several studies.

29. **If an application fails to include both genders or minority groups and this is not appropriately justified, how much should the priority score be affected?**

The priority score is based on a scientific/technical evaluation, using published review criteria. The review criteria include not only the adequacy of plans to include both genders and racial/ethnic groups, but all of the standard criteria, such as adequacy of research plan, adequacy and appropriateness of training and experience of investigators and staff, and importance and scientific significance of the problem to be studied.

Because of the nature of scientific evaluation of grant and cooperative agreement applications, none of the review criteria is pre-assigned a specific weight, and reviewers are asked to weigh all of the criteria in the context of the research being proposed, giving each the importance appropriate for the specific work proposed. Any one criterion may be given a high or low weighting by each reviewer depending on its importance in the particular research being proposed.

(See Sections III.C. and IV.C.3. in the NIH Guidelines)

30. **How does the inclusion policy apply to research contract proposals and projects?**

The inclusion policy applies to NIH research and development contract projects as well as grant and cooperative agreement projects. However, there are some differences in procedures as a result of the federal acquisition regulations for contracting.

The description of the planned contract project is provided in the Request for Proposals (RFP), which includes the statement of work and the evaluation criteria. When planning and preparing the RFP, the NIH project officer must address many issues, including determining whether the project will be a clinical research project, and whether it will be an NIH-defined clinical trial; the study design, sample size issues, the inclusion requirements for both genders and minority groups, and outreach plans need to be addressed, and appropriate justifications provided when the requirement is for limited representation. The required review criterion should be included as part of the evaluation criteria published in the RFP.

The investigator responding to the RFP must address the inclusion policy as reflected in the RFP requirements and evaluation criteria. Peer reviewers will evaluate proposals, looking at plans for recruitment, retention and outreach for study participants, using the published review criteria.

(See Sections III.C., IV.A. and IV.G. in the NIH Guidelines)

E. AWARDS

31. **How will conformance to this policy affect funding of projects?**

Regardless of the priority score, percentile ranking or program relevance of the proposed research, the NIH funding components will not fund grants or award contracts that do not comply with this policy.

(See Section III.C. in the NIH Guidelines)

32. **Does the policy apply to foreign projects funded by the NIH?**

The NIH policy on inclusion of women in research conducted outside the United States is the same as that for research conducted in the United States. However, with regard to the population of the foreign country, the definition of the minority groups in foreign countries may be different than in the United States. If there is scientific rationale for examining subpopulation group differences within the foreign population, investigators should consider designing their studies to accommodate these differences.

(See Section IV.C.9. in the NIH Guidelines)

33. **How do the new Guidelines impact on Institutional Review Boards (IRBs)?**

IRBs have long had as part of their responsibilities examining ethical issues and determining equitable selection of subjects in accordance with the regulations for protection of human subjects [45 CFR 46.111(a)(3)]. The inclusion of both women and men and of minorities in research (intramural and extramural) is important, both to ensure that they receive an appropriate share of the benefits of research and that they do not bear a disproportionate burden. To the extent that participation in research offers direct benefits to the participants, underrepresentation of men, women, or minorities denies them the opportunity to receive this benefit. Moreover, for purposes of generalizing research results, investigators must include the widest possible range of population groups.

The Office for Protection from Research Risks has discussed the impact of this policy in OPRR Reports, Number 94-01, April 25, 1994, which has been distributed to IRBs. Seven points to consider in deliberations about appropriate selection of research participants are offered. IRBs

are empowered (by 45 CFR Part 46, the DHHS assurances, and the NIH Guidelines) to approve, request modification of, or disapprove research based on their review. Copies of the OPRR Reports may be obtained from OPRR or your IRB.

(See Section IV.C.2. in the NIH Guidelines)

34. **How do we report on inclusion of women and minorities?**

Applicants will provide information in applications, proposals, and progress reports using the following summary table format for planned enrollment of women and minorities. Awardees will report annually on the actual enrollment for the approved project using the same format.

SUMMARY TABLE. GENDER AND MINORITY INCLUSION IN RESEARCH

Study title:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female							
Male							
Unknown							
Total							

Note: For planned studies, indicate the expected study composition using the categories noted below. For ongoing studies, provide the number of subjects enrolled in the study to date (cumulatively since the most recent competitive award) according to the categories in the summary table. If there is more than one study, provide a separate table for each study. In addition, indicate the planned or actual minority subpopulations that are included in the study.

(See Section III.C. in the NIH Guidelines)

35. **When does the policy begin to apply?**

This policy applies to all applications, proposals, and intramural projects submitted on and after June 1, 1994, (the date of full implementation). Projects funded prior to June 10, 1993, must still comply with the 1990 policy and report annually on enrollment of subjects in contracts and in intramural projects using gender and racial/ethnic categories as required in the Application for Continuation of a Public Health Service Grant (PHS Form 2590).

(See Section IV.A. in the NIH Guidelines)

36. **Where can I obtain additional information?**

Additional information may be obtained from NIH staff identified in Request for Applications (RFAs), Program Announcements (PAs), or on awards. The following senior extramural staff from the NIH Institutes and Centers may be contacted for more information about the policy and relevant Institute/Center programs:

Dr. Marvin Kalt
National Cancer Institute
6130 Executive Boulevard
Executive Plaza North, Room 600A
Bethesda, Maryland 20892
Tel: (301) 496-5147

Dr. Ralph Helmsen
National Eye Institute
6120 Executive Boulevard
Executive Plaza South, Room 350
Bethesda, Maryland 20892-7164
Tel: (301) 496-5301

Dr. Lawrence Friedman
National Heart, Lung, and Blood Institute
6701 Rockledge Drive
2 Rockledge Center, MSC 7938
Bethesda, Maryland 20892
Tel: (301) 435-0422

Dr. Miriam Kelty
National Institute on Aging
7201 Wisconsin Avenue
Gateway Building, Room 2C218
Bethesda, Maryland 20892
Tel: (301) 496-9322

Dr. Cherry Lowman
National Institute on Alcohol
Abuse and Alcoholism
6000 Executive Boulevard
Bethesda, Maryland 20892
Tel: (301) 443-0796

Dr. George Counts
National Institute of Allergy
and Infectious Diseases
6003 Executive Boulevard
Solar Building, Room 4B04
Bethesda, Maryland 20892
Tel: (301) 496-8697

Dr. Julia Freeman
National Institute of Arthritis
and Musculoskeletal and Skin Diseases
45 Center Drive, MSC 6500
Building 45, Room 5AS19F
Bethesda, Maryland 20892-6500
Tel: (301) 594-5052

Ms. Hildegard Topper
National Institute of Child Health
and Human Development
9000 Rockville Pike
Building 31, Room 2A-03
Bethesda, Maryland 20892
Tel: (301) 496-0104

Dr. Craig Jordan
National Institute on Deafness
and Other Communication Disorders
6120 Executive Boulevard
Executive Plaza South, Room 400C
Bethesda, Maryland 20892-7180
Tel: (301) 496-8693

Dr. Norman S. Braveman
National Institute on Dental Research
45 Center Drive
Building 45, Room 4AN24
Bethesda, Maryland 20892
Tel: (301) 594-2089

Dr. Paul Coates
National Institute of Diabetes
and Digestive and Kidney Diseases
45 Center Drive
Building 45, Room 5AN24J
Bethesda, Maryland 20892
Tel: (301) 594-8805

Ms. Eleanor Friedenberg
National Institute on Drug Abuse
5600 Fishers Lane
Parklawn Building, Room 10-42
Rockville, Maryland 20857
Tel: (301) 443-2755

Dr. Gwen Collman
National Institute of Environmental
Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina
27709
Tel: (919) 541-4980

Dr. Alison Cole
National Institute of General
Medical Sciences
45 Center Drive, MSC 6200
Building 45, Room 2AS49K
Bethesda, Maryland 20892-6200
Tel: (301) 594-1826

Dr. Dolores Parron
National Institute of Mental Health
5600 Fishers Lane
Parklawn Building, Room 17C-14
Rockville, Maryland 20857
Tel: (301) 443-2847

Dr. Constance Atwell
National Institute of Neurological
Disorders and Stroke
7550 Wisconsin Avenue
Federal Building, Room 1016
Bethesda, Maryland 20892-9190
Tel: (301) 496-9248

Dr. Mark Guyer
National Center for Human
Genome Research
9000 Rockville Pike
Building 38A, Room 604
Bethesda, Maryland 20892
Tel: (301) 402-5407

Dr. Lynn M. Amende
National Institute of Nursing Research
45 Center Drive, MSC 6300
Building 45, Room 3AN12
Bethesda, Maryland 20892
Tel: (301) 594-5968

Dr. Harriet Gordon
National Center for Research Resources
6705 Rockledge Drive, MSC 7965
1 Rockledge Center, Room 6030
Bethesda, Maryland 20892-7965
Tel: (301) 435-0790

Johnnie Smith
Fogarty International Center
31 Center Drive, MSC 2220
Building 31, Room B2C39
Bethesda, Maryland 20892
Tel: (301) 402-9590

37. **What are the initial review group codes for inclusion of women and minorities in clinical research?**

The codes are as follows:

HEADER OUTPUT FOR SUMMARY STATEMENTS

- Clinical Research
  - (X) Clinical Trial, Gender, and Minority Codes not assigned* (for non-clinical research or non-scored applications)
  - (Y) NIH-defined Phase III Clinical Trial*
  - (N) Clinical Research—not an NIH-defined Phase III clinical trial*

- Gender
  - G1A Includes both genders, scientifically acceptable
  - G2A Includes only women, scientifically acceptable
  - G3A Includes only men, scientifically acceptable
  - G4A Gender representation unknown, scientifically acceptable

  - G1U Includes both genders, but scientifically unacceptable
  - G2U Includes only women, scientifically unacceptable
  - G3U Includes only men, scientifically unacceptable
  - G4U Gender representation unknown, scientifically unacceptable

- Minority
  - M1A Includes minorities and non-minorities, scientifically acceptable
  - M2A Includes only minorities, scientifically acceptable
  - M3A Includes only non-minorities, scientifically acceptable
  - M4A Minority representation unknown, scientifically acceptable

  - M1U Includes minorities and non-minorities, but scientifically unacceptable
  - M2U Includes only minorities, scientifically unacceptable
  - M3U Includes only non-minorities, scientifically unacceptable
  - M4U Minority representation unknown, scientifically unacceptable

** these codes do not appear in header*